

2013 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



PART V: ACTIVITIES OF MEMBER STATES AND OTHER EUROPEAN COUNTRIES IN THE FIELD OF RARE DISEASES

This work was financed by the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01

This document has been produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD, formerly the European Commission's Rare Diseases Task Force) through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01, Coordinator: Kate Bushby, University of Newcastle, United Kingdom), within the European Union's Second Programme of Community Action in the Field of Health.

More information on the European Union Committee of Experts on Rare Diseases can be found at www.eucerd.eu.

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To quote this document:

Aymé S., Rodwell C., eds., "2013 Report on the State of the Art of Rare Disease Activities in Europe", July 2013.

<http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesV.pdf>

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ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2012. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2012

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Each part contains the following description of the methodology, sources and validation process of the entire report, and concludes with a selected bibliography and list of persons having contributed to the report.

1. METHODOLOGY AND SOURCES

The main sources of data for the update of the present report were those collected through the systematic surveillance of international literature and the systematic query of key stakeholders carried out in order to produce the OrphaNews Europe newsletter, various reports published by the European Commission (including past reports of the workshops of the EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products. The principal information sources and the collection of data are described in detail here below.

- **European Commission websites and documents**

Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health¹ and Directorate General Research CORDIS website² as well as the site of the European Medicines Agency³, in particular the pages of the COMP⁴ (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe⁵ newsletter for the 2012 period was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the

¹ http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

² http://cordis.europa.eu/home_fr.html

³ www.ema.europa.eu

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30

⁵ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France⁶ (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **EUCERD Publications**

Parts III, IV and V of this report present an update of the information previously published in the 2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD⁷ (July 2010), 2011 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases⁸ and the 2012 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases⁹. The methodology for the production of these previous reports is outlined in their respective introductions. In addition, reports from previous workshops of the EUCERD, including the EUCERD Joint Action have been used.

- **Reports of the EUCERD meetings**

The reports of 2012 meetings of the EUCERD were used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2011.

- **Reports on orphan medicinal products**

The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹⁰ published in 2006 by the European Commission and produced using data collected by the EMA and Orphanet. This information has been updated when information is available and quoted when still applicable. Another valuable source of information on Orphan Drug policy, at EU and Member State levels was the 2009 KCE 112B report published by the KCE-Belgian Federal Centre of Healthcare Expertise (*Federaal Kenniscentrum voor de Gezondheidszorg/Centre federal d'expertise des soins de santé*) entitled "*Orphan Disease and Orphan Drug Policies*" (*Politiques relatives aux maladies orphelines et aux médicaments orphelins*)¹¹. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document "*Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)*" also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V was added to the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*¹² by Donald Macarthur: this report is referenced in footnotes when used.

⁶ <http://www.orpha.net/actor/cgi-bin/OAhome.php>

⁷ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

⁸ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesI.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

⁹ <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesI.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>

¹⁰ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

¹¹ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

¹² <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

- **EURORDIS website and websites of national alliances of patient organisation**

The site of EURORDIS, the European Organisation for Rare Diseases¹³ was used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day 2012 site¹⁴, maintained by EURORDIS, also provided information on events at Member State level¹⁵ concerning Rare Disease Day.

- **Orphanet**

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials, patient organisations and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links¹⁶ to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The national Orphanet websites were also consulted to gather national events and initiatives.

A selected bibliography and contributions are provided at the end of each volume of the report.

2. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the European Union Committee of Experts on Rare Diseases, 2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases and 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*) which have covered activities up to the end of 2011. The present edition takes into account advances and activities in the field of rare diseases and orphan medicinal products at EU and MS level in 2012.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in February 2013 to EUCERD Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: representatives at the EUCERD in the respective countries and their alternates, the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2012 to be included in Part II. Final validation of Parts II, V, VI concerning their country were sent to the EUCERD Member State representatives for final validation, to the best of their knowledge, in May 2013.

Part III and IV of the report on activities at European Union level was sent for validation, to the best of their ability, by the representatives at the EUCERD of the European Commission Directorate Generals for Health and Consumers, Research and Innovation, Enterprise and Industry, and the European Medicines Agency (EMA) respectively: this process was carried out in March/April 2013 by the Scientific Secretariat of the EUCERD. The

¹³ <http://www.EURORDIS.org/secteur.php3>

¹⁴ <http://www.rarediseaseday.org/>

¹⁵ <http://www.rarediseaseday.org/country/finder>

¹⁶ http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

European Commission and its agencies are not responsible, however, for the completeness and the accuracy of the information presented in this report. The new activities in 2012 were extracted and added to Part II.

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was drafted by the Scientific Secretariat of the EUCERD and then sent to all EUCERD members and their alternates for their input before publication in May 2013.

3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level; Part II is an extraction of the developments at EU and MS level in 2012 based on Parts III, IV and V; Part III concerns activities of the European Commission; Part IV concerns European Medicines Agency activities and other European activities/events at European level apart from the activities of the European Commission; Part V concerns activities at EU MS level, as well as five other non-EU European countries where information was available; Part V provides the content of Parts II and V in individual country-specific reports.

Each part is followed by a selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when in place. Each part is also followed by a list of contributors the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts III, IV and V, which serve to provide more detailed background information at EU and MS level. The overview is structured into a number of topics: political framework, expert services in Europe, research and development, orphan medicinal products and therapies for rare diseases, patient organisations and information services.

Part II is a new section of the report, providing information extracted from Parts III, IV and V, relative only to the new activities and initiatives reported for the year 2012.

Part III of the report focuses on activities in the field of rare diseases at EC level is split into four sub-sections:

1. EC activities related to rare diseases in the field of public health;
2. EC activities related to rare diseases in the field of research;
3. EC activities in the field of orphan medicinal products and therapies for rare diseases.

The sub-section concerning the EC activities actions in the area of Public Health is divided into three parts: an overview of DG Health and Consumers' activities in the field of public health, activities in the field of rare diseases funded by DG Health and Consumers, and activities of DG Health and Consumers indirectly related to rare diseases. The sub-section concerning the EC activities in the field related to research in the field of rare diseases presents information concerning DG Research and Innovation's 5th, 6th and 7th framework programmes for research, technological development and demonstration activities related to rare diseases, as well as information concerning the International Rare Disease Research Consortium (IRDiRC).

Part IV of the report contains information on the activities in the field of rare diseases of the EMA and other rare disease activities at the European level, including selected transversal EU activities and conferences at European level:

- European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases, EMA Committee for Orphan Medicinal Products' activities, EMA Committee on Human Medicinal Products' activities, European legislation and activities in the field of clinical trials, European legislation and activities in the field of advanced therapies, European legislation and activities in the field of medicinal products for paediatric use, other EMA activities and initiatives relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.
- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2012.

Part V concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Iceland, Norway and Switzerland in addition to Croatia and Turkey as candidates for EU membership, as well as Israel. These sections are organised in alphabetical order by country.

The information on each country is clearly divided into a number of categories:

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise¹⁷
- Registries
- Neonatal screening policy
- Genetic testing¹⁸
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Good practice guidelines
- Training and education initiatives
- National rare disease events in 2012¹⁹
- Hosted rare disease events in 2012²⁰
- Research activities (National research activities, Participation in European research projects²¹, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability²², Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products), Other therapies for rare diseases
- Orphan devices
- Specialised social services

The categories for which information is provided depend wholly on the information available following data collection from the described sources and contact with stakeholders. If no detail has been given for a topic, the mention "no specific activity/information reported" has been added.

¹⁷ The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

¹⁸ This section contains data extracted in December 2012 from the Orphanet database of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term 'estimated' is used as the concept of a single disease is a variable one).

¹⁹ As announced in OrphaNews Europe.

²⁰ As announced in OrphaNews Europe.

²¹ Past and ongoing participation in DG Research and Innovation financed projects. Some countries have added information on additional European projects.

²² Contacts were asked to provide information on availability of orphan medicinal products (i.e. which drugs are launched on the market/sold at national level). As this information is often hard to identify, some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case which of these concepts is being referred to.

Part VI concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Iceland, Norway and Switzerland in addition to Croatia and Turkey as candidates for EU membership, as well as Israel. This section is the same as Parts II and V, except that the information is presented as a separate document for each country to facilitate dissemination at country level.

Each section has two parts: firstly the state of the art up until the end of 2012, and secondly the state of the art of activities in 2012 only so as to easily identify new actions and activities.

1. EUROPEAN UNION MEMBER STATES

1.1. AUSTRIA

Definition of a rare disease

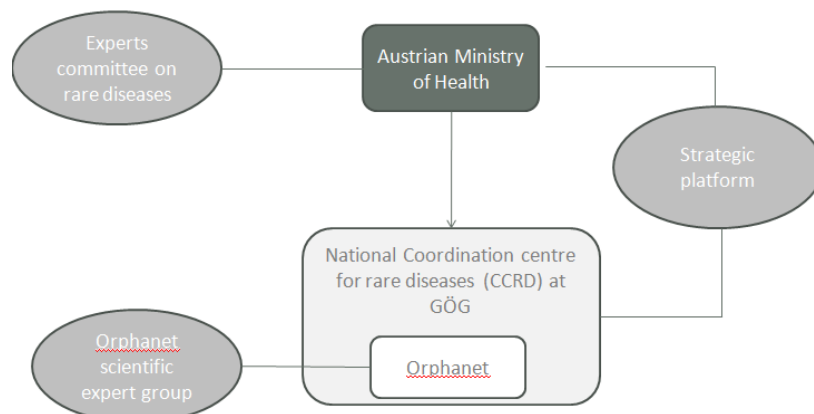
In 2012 there was still no official definition of rare diseases in Austria; on an informal basis, stakeholders in Austria accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 persons. In the national plan of action (still under development; see below) it is foreseen to officially adopt the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

In response to a petition by health professionals and patient organisations for a national action plan on rare diseases in Feb 2008 and considering the recommendations of the European Council of 8 June 2009 to implement a national action plan on rare diseases until 2013 the Highest Austrian Health Advisory Board (“Oberster Sanitätsrat”) of the Austrian Ministry of Health (BMG) established a subcommittee for rare diseases in May 2009, consisting of 17 members from 13 different organisations or institutions (covering the main stakeholders in the field). This working group was managed by the Austrian Orphanet team and laid the foundation for a national plan of action for rare diseases. It was the first time in Austria that an expert committee of this size, covering a broad spectrum of viewpoints, was working on rare diseases in a comprehensive manner, with topics ranging from the description of the situation of rare diseases in general to legal and ethical aspects, equality in legal and practical terms, the identification of concrete problems, bottlenecks and restrictions that patients, relatives, physicians and scientists are confronted with, and, finally, the identification of possible measures and strategies aiming to improve the situation, to combat (structural) deficits, to optimise health care pathways, and to minimise disease burden wherever possible.

However, due to the many topics on the agenda and the lack of resources of the Board Members the Austrian Ministry of Health decided to establish a National Coordination Centre for Rare Diseases (CCRD, Nationale Kontaktstelle für Seltene Erkrankungen, NKSE). The CCRD was established on 1 January 2011 at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG) and has currently in 2012 a team of 1.2 full time equivalents. It also integrates part of the Austrian Orphanet team. Most members of the subcommittee for rare diseases (including patient representatives, physicians and representatives of social health insurance and industry) are still involved in the topic as they kindly accepted their appointment to the Expert committee on rare diseases that was established in mid 2011 by the Ministry of Health (see Figure 1 below). In addition a strategic platform with delegates of the Ministry of Health, representatives of the regions and payers (Austrian provinces and the Main association of the Austrian social security institutions) was set up. In 2012 these two platforms continued its active participation in the development of the national plan for rare diseases.

Figure 1: Organisational Chart of the Austrian CCRD



The establishment of the CCRD was one of the first steps of the development of a national plan for rare diseases as proposed by the subcommittee for rare diseases in November 2010. The founding of CCRD included a sustained funding until the end of 2013 of Orphanet as the national information system for rare diseases and the involvement of both, the Medical University of Vienna and the GÖG as partners in the Joint Action Orphanet Europe.

The main activities of the CCRD in 2012, were the following:

- Acting as the main driving force in drawing the national plan for rare diseases until the end of 2013 through a participative process of discussing the 9 priorities of the national plan with all representatives of the expert group as well as of the strategic platform;
- Publication of the first report on rare diseases in Austria based on a large scale needs assessment survey involving academics, stakeholders such as patients, physicians, payers and industry. The report (only available in German) can be downloaded on the website of the Ministry of Health²³ or on the website of the CCRD²⁴;
- Awareness raising among professionals / experts / doctors / patients on the topic of rare diseases through presentations and dissemination of information;
- Acting as the focal point for European activities in the field of rare diseases through active participation in EU-funded projects and initiatives such as Orphanet and EUCERD and the Cross Border Health Care Directive as well as other European initiatives in the area of Orphan Medical Products (e.g. the EU Working Group on Mechanisms for a coordinated access to orphan medicinal products as part of the platform for Access to Medicines in Europe which is part of the Corporate Social Responsibility Process launched by Commissioner Tajani);
- Continuation of Orphanet activities:
 - Establishment of Orphanet national scientific advisory board;
 - Updating of national Orphanet website;
 - Dissemination of information on rare diseases in Austria ;
- Agreement on eligibility criteria for the establishment and designation of centres of expertise based on EUCERD recommendations; these criteria will be included in the Austrian Health Care Structure Plan, which is a nation-wide planning tool;
- Acting as the communication hub between actors in the field, focusing on health care professionals and other stakeholders.

At the second Austrian National Conference on Rare Diseases, which took place on 4-5 October 2012 in Salzburg among other topics the eligibility criteria for the establishment and designation of centres of expertise were presented.

The National Plan for Rare Diseases will be published in autumn 2013.

Centres of expertise

Currently, there are no officially designated centres of expertise in Austria; informally, a few well-recognised centres exist with an outstanding expertise in their field, the best known probably being the “EB (Epidermolysis bullosa) house Austria in Salzburg. The Austrian Ministry of Health supports the concept of such centres and has asked the CCRD to work on this topic.

In 2012 an agreement was reached on the definition of eligibility criteria for the establishment of centres of expertise. These criteria take into account the recommended EUCERD criteria as well as national healthcare regulations. These criteria will be included in the national plan for rare diseases which will be published in autumn 2013. It is therefore expected that the developed criteria will be embedded in the Austrian health care structure plan, which will also specify the designation of future centres of expertise.

Registries

Currently, no nationwide, general, comprehensive registry for rare disease patients exists in Austria. There is no designation process for rare disease registries in Austria at the moment; however it is foreseen that the national plan for rare diseases will include criteria for the designation of registries. Approximately 25 registries or bio-banks for individual rare diseases or groups of rare diseases are run by specialised clinics or networks of experts from different clinics, e.g. a haemophilia registry or one for acromegalia. These registries are primarily maintained on a private/institutional basis, in many instances “in kind” by the expert teams; some registries are

²³ http://bmg.gv.at/home/Schwerpunkte/Krankheiten/Bericht_Seltene_Erkrankungen_in_Oesterreich

²⁴ <http://www.goeg.at/de/BerichtDetail/Seltene-Erkrankungen-in-Oesterreich-2012.html>

additionally supported by corresponding patient support groups. Some of the European registries Austrian teams participate in are EUROCARE CF, AIR, RARECARE, EIMD, EMSA-SG, EUROCAT, SCNIR and ENRAH. Actions in this area are included in the National Plan for Rare Diseases (“National/Cross-border registry”).

Neonatal screening policy

Since the late 1960s, Austria has a well-established, nationwide newborn screening (NBS) program that is carried out for practically all newborns in one screening centre, operated by the University Children’s Hospital of the Medical University of Vienna. The Austrian NBS program is one of the most comprehensive programs worldwide and screens for the following 32 diseases and conditions: adrenogenital syndrome, biotinidase deficiency, carnitine-acylcarnitine translocase deficiency, carnitine palmitoyl transferase IA deficiency, carnitine palmitoyl transferase II deficiency, carnitine uptake deficiency, citrullinemia, argininosuccinic aciduria, congenital hypothyroidism, cystic fibrosis, galactosemia, glutaric acidemia type I, glutaric acidemia type II / multiple acyl-CoA dehydrogenase deficiency, homocystinuria and hypermethionemia, isobutyryl CoA dehydrogenase deficiency, isovaleric acidemia, β -ketothiolase deficiency, long-chain acyl-CoA dehydrogenase deficiency, mitochondrial trifunctional protein deficiency, maple syrup urine disease, medium-chain acyl-CoA dehydrogenase deficiency, methylmalonic aciduria, propionic acidemia, holocarboxylase synthetase deficiency, phenylketonuria and hyperphenylalaninemia, short-chain acyl-CoA dehydrogenase deficiency, tyrosinemia type I, very long-chain acyl-CoA dehydrogenase deficiency, 2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency, 3-Hydroxy-3-methylglutaric aciduria, 3-Methylcrotonyl-CoA carboxylase deficiency, and 3-Methylglutaconic aciduria type I. This screening panel remained unchanged in 2012.

Since 2009, and further expanded in 2010, a scientifically based NBS exists that covers six different lysosomal storage disorders (e.g. Mucopolysaccharidosis (MPS) type 1, Gaucher, Fabry, Pompe, and Nieman-Pick Type A/B). At end of 2011 it had not been decided whether (and when) any of these diseases should be included in the national program.

Detailed information regarding the Austrian NBS is provided by a completely revised homepage²⁵ that was made available online at the end of 2011 and that is available in three languages (German, English, and Turkish). As additional service, nearly all diseases listed and explained on the NBS homepage are directly linked to the relevant disease entity in the Orphanet database.

Genetic Testing

Molecular genetic testing in Austria is regulated by the so-called “Gentechnikgesetz” (GTG), first established in 1994²⁶ and last revised in 2005²⁷. The Gentechnikgesetz covers all legal, ethical and (bio-) safety aspects regarding diagnostics and research in the field of molecular genetics (including generation and handling of genetically modified organisms). In the chapter on human molecular genetic testing, genetic tests are subdivided into the following four types:

- (a) Type 1 comprises tests to identify either concrete somatic changes in the number, structure, or sequence of chromosomes, genes or DNA fragments or concrete chemical modifications in chromosomes, genes or DNA fragments in patients suffering from a clinically manifested and diagnosed disease (for instance, the search for a somatic mutation or altered methylation status in a tumour tissue sample);
- (b) Type 2 covers tests searching for germline mutations in patients suffering from a clinically manifested and diagnosed disease;
- (c) Type 3 comprises tests to establish the genetic risk/predisposition of a healthy individual to potentially develop a genetic disease in the future, or to establish the carrier status of a healthy individual for a certain genetic disease, in disorders where prophylaxis or treatment are available;
- (d) Type 4 covers tests to establish the genetic risk/predisposition of a healthy individual to potentially develop a genetic disease in the future, or to establish the carrier status of a healthy individual for a certain genetic disease, in disorders where prophylaxis or treatment do not exist.

While for genetic tests of categories 1 and 2 no authorisation is necessary, tests of categories 3 and 4 can only be performed in laboratories officially authorised by the Austrian Ministry of Health. Institutions seeking authorisation have to register their activity and apply with a detailed description of their laboratories, equipment, technical procedures, quality schemes, and experience in genetic testing. The formal authorisation

²⁵ <http://www.meduniwien.ac.at/hp/neugeborenen-screening/>

²⁶ http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/510_1994.pdf

²⁷ <http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/gtg-nov.11-05.pdf>

for the respective genetic test is granted after an evaluation process, which includes consultation of the scientific board of the Committee on Gene Technology (“Gentechnikkommission”).

Laboratories performing genetic testing in Austria are listed in a special registry (“Genanalyseregister”) administrated by the Ministry of Health. Of note, the designation “reference laboratory” as an official term does (currently) not exist in Austria.

In Austria, reimbursement is primarily a responsibility of the individual states (“Bundesländer”) and not centrally regulated (of note, some exceptions exist). This responsibility is further split between two different types of institutions, depending on whether the patient had been treated (a) in the hospital sector (as inpatient or outpatient) or (b) in the private sector (i.e. by a general practitioner or consultant of a specific medical discipline that has his own practice and a service contract with the relevant health insurance fund). In the first case, the costs of any type of diagnostic test or treatment have to be paid from the budget of the hospital. The hospital, in turn, is indirectly reimbursed by the health fund of the respective state (“Landesgesundheitsfonds”) on DRG basis. However, hospitals have to make efforts to not exceed the budgets allotted to them for each calendar year. In the second case (private practice), reimbursement is the responsibility of the sickness fund of the patient. In this instance, specific tariffs are calculated by the sickness fund for each type of service and services are reimbursed according to the tariff catalogue. Basically, mainly services that have been successfully negotiated with the sickness fund and integrated into their individual tariff catalogue are eligible for reimbursement. Still, patients/their doctors have always the possibility to apply for individual reimbursement.

Taking into account this dual reimbursement system with all its regulations, the reimbursement of genetic testing is as follows:

- (a) As an obligatory prerequisite, all tests have to be officially accepted/approved by the (local) sickness fund of the patient and integrated into their tariff catalogue (either as a specific single test, or on the basis of average calculations for long versus short genes, number of exons, complexity of the analysis, or other criteria);
- (b) For in- and outpatients, the hospital covers the costs according to the tariffs of the laboratory performing the test;
- (c) For patients in the private practice, the respective insurer carries the costs; however, it is possible that certain analyses (depending on the internal regulations of the sickness fund) require an ex-ante approval by the head physician (“Chefarzt”) of the health insurance, even if the analysis is requested/recommended by a specialist for human genetics (in Tyrol, for instance, all genetic analyses that cost more than €1.000 need to be authorised by a health insurance “Chefarzt”).

Genetic testing abroad is possible as soon as the test is strongly indicated for an individual patient and cannot or not easily be performed within the country (again, the same rules apply as above and the determination has obligatorily to be approved ex-ante either by the respective insurance fund or – for inpatients - by the medical director of the hospital).

Diagnostic tests are registered as available in Austria for 632 genes and an estimated 609 diseases in the Orphanet database²⁸.

National alliances of patient organisations and patient representation

Pro Rare Austria was established on 3 December 2011. This national “Allianz für seltene Erkrankungen was founded by Dr. Riedl, chairman of DEBRA Austria, the Epidermolysis bullosa patient support group.

In 2012 Pro Rare Austria achieved the following milestones:

- Development of a cooperate identity for Pro Rare Austria including a logo, claim, banners and roll-ups;
- Publications in media - more than 30 newspaper articles and TV broadcasts;
- Fundraising for and organisation of the Rare Disease Day 2012 with around 400 participants;
- Development and launch of website: www.prorare-austria.org;
- Out of around 60 rare disease patient organisation, 20 organisations are members of Pro Rare Austria;
- Member of EURORDIS;
- Participation of EURORDIS Summer School in Barcelona in June 2012;
- Active participation at the meetings of the expert committee on rare diseases under the lead of the national coordination centre for rare diseases;
- Questionnaire for patients about the key challenges of patients with rare diseases;
- Establishment of a medical expert committee.

²⁸ Information extracted from the Orphanet database in December 2012.

Apart from Pro Rare general alliances of patient organisations (both for rare and non-rare diseases) do exist on the state level (ARGE Selbsthilfe Carinthia, Upper Austria, Lower Austria, Salzburg, Styria, Tyrol, Vorarlberg, and Vienna). They are united under the supra-umbrella *Arbeitsgemeinschaft (ARGE) Selbsthilfe*, which is located in Vienna. The *ARGE Selbsthilfe* can provide limited funding (up to €900 for a period of 6 months with repeat applications possible) for all patient organisations (including those in the rare diseases field), however, funding is confined to support the formation of a new patient organisation or to provide interim aid for an existing one bridging a limited time gap. The Austrian Health Institute supports Pro Rare by providing meeting rooms and optional funding for further education in the field.

Thematically restricted support for patient organisations will possibly be part of the future National Plan for Rare Diseases, integrated into the priority “Improving awareness and knowledge about rare diseases”.

Sources of information on rare diseases and national help lines

Orphanet activities in Austria

With the establishment of the National Coordination Centre for Rare Diseases (CCRD) the dedicated Austrian team that was in charge for Orphanet for almost ten years expanded to include GÖG staff members. Part of the staff is still hosted by the Institute of Neurology at the Medical University of Vienna. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, bio-banks, clinical trials and patient organisations) in Austria for entry into the Orphanet database. The reason for including two institutions in the Orphanet work is to guarantee long-term sustainability of the Orphanet activities in the Austrian health care system. Therefore, the teams work closely together.

In 2011, the Orphanet-Austria²⁹ national website which provides an entry point to the Orphanet database was launched based on the self-developed country website which was launched back in 2008. The objectives are to provide basic information on the Orphanet database and the local Orphanet team, as well as to raise public awareness on rare diseases in general. The team reports about major events and activities organised either by Orphanet Austria itself or by other stakeholders.

Official information centre for rare diseases

Until 2010, Orphanet was the only official source of information specific to rare diseases in Austria. With the establishment of the National Coordination Centre for Rare Diseases (Nationale Koordinationsstelle für Seltene Erkrankungen, NKSE) at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG³⁰) in January 2011 an official information platform for all stakeholders was established. The CCRD is funded by the Austrian Ministry of Health (Bundesministerium für Gesundheit) and shall act in the mid-time as information provider next to its other functions. Orphanet Austria was integrated into this coordination centre to enable maximum synergy between the two structures. In the first phase the CCRD launched the Austrian orphanet website³¹ and provided information to health professionals, e.g. by presenting on rare disease specific congresses and events.

Help line

Currently, there is no official nation-wide national helpline for rare diseases in Austria. In the last couple of years individual regional activities developed such as the helpline in Salzburg, focusing primarily on rare genetic skin disorders (genodermatoses) and metabolic disorders.

Other sources of information

Further sources of information on rare diseases include:

- Disease-specific websites of patient organisations. A number of patient organisations for specific rare diseases – or groups of rare diseases – exist in Austria that host excellent websites providing extensive and very detailed information on “their” rare disease/group of rare diseases (including information on the medical background, symptoms, diagnostics and treatment/care of patients)³².
- A number of medical departments or patient registries also host websites with comprehensive and useful information on those rare diseases they are focusing on³³.

²⁹ <http://www.orpha.net/national/AT-DE/index/startseite/>

³⁰ <http://www.goeg.at/de/Bereich/Koordinationsstelle-NKSE.html>

³¹ www.orpha.net/national/AT-DE/index/startseite

³² Some examples (non-exhaustive) are <http://www.mps-austria.at>, <http://www.klinefelter.at>, <http://www.rett-syndrom.at/index.html>, <http://www.debra-austria.org>, <http://www.pah-info.at>

³³ Some (non-exhaustive) examples are: www.genodermatosen.at, <http://www.akromegalie-register.at/wDeutsch/akromegalie/index.php?navanchor=1110006>, <https://www.studienregister.at/web/guest/home> (select info folder for haemophilia).

- The Austrian Ministry of Health³⁴ as well as the website of the National Coordination Centre for Rare Diseases (CCRD)³⁵ provide general information on rare diseases in Austria.
- Rare disease-specific information is also published on the official governmental health platform of Austria. Provided information include: a link to the report on rare diseases, as well as information regarding the establishment of the CCRD³⁶.

Good practice guidelines

In several medical disciplines good practice guidelines exist or are worked on for individual rare diseases.

Training and education initiatives

The Academy of the Epidermolysis Bullosa House AUSTRIA hosts training workshops for epidermolysis bullosa on a regular basis. In addition, the Department of Dermatology of the Paracelsus Medical University Salzburg organised the "Fostering Courses for Genodermatoses" under the auspices of the European Academy of Dermatology and Venerology in 2009, 2010 and 2012.

National rare disease events in 2012

A number of events were held to mark the Rare Disease Day 2012 with Pro Rare leading the organisation of this day in Austria. Events to mark the day included an information day on 26 February 2012 in Salzburg, and a march for rare diseases in Vienna on 3 March 2012.

On 4-5 October 2012, the Second Austrian National Conference on Rare Diseases was organised in Salzburg. The Days of Molecular Medicine (8-10 October 2012 in Vienna) were dedicated to rare genetic disorders, as a professional exchange on latest scientific developments in the field of rare genetic diseases.

Hosted rare disease events in 2012

Amongst the hosted events in 2012 announced in *OrphaNews Europe* was the Days of Molecular Medicine 2012 Conference: The Translational Science of Rare Diseases - From Rare to Care (Vienna, 8-10 October 2012).

Research activities and E-Rare partnership

National research activities

Currently, there is no specific and explicit funding policy for rare diseases in Austria. In theory, funding is available through grant applications at different funding bodies (for instance, the Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund; FWF), the Nationalbank, or minor resources such as the Fonds des Bürgermeisters der Bundeshauptstadt Wien); however, funding follows a bottom-up approach, meaning that applications from all medical disciplines and, in some instances, totally unrelated medical, as well as non-medical, research fields compete each other in a peer-review selection process, harbouring the risk (in times of restricted research budgets) of a selection bias towards projects addressing more common diseases.

An alternative source of funding is provided by occasional project calls launched by the Austrian Ministry of Science. In the past 5 years, one of these calls was dedicated to rare diseases. Moreover, several fundraising patient organisations finance rare disease research projects. One strategic priority in the Austrian national plan will be the implementation of a defined, separate funding budget in the main existing research bodies, which will be specifically dedicated for research on rare diseases, as aforementioned in the National Plans segment ("Establishing a selective funding for research on rare diseases").

Participation in European research projects

Austrian teams participate, or have participated, in around 50 European research projects or research networks for rare diseases – with a leading role in eight – including for instance: ACADEMIC GMP, BNE, CLINIGENE, DIRECT, EDEN, EMSA-SG, EFACTS, EMINA, ENCCA, EMINA-2, ENRAH, ENCE-PLAN, EURIPFNET, EUROTRAPS, EURO-IRON1, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROWILSON, GENEGRIFT, GENESKIN, GENOMIT, IMMOMEK, IntReALL, IMMOMEK, INTREALL, LEUKOTREAT, LYMPHANGIOGENOMICS, MYELINET, NEUTRONET, NEUROPRION, OPTATIO, OPTIPS, PERXISOMES, PNSEURONET, PROTHETS, PULMOTENSION, PWS, RD-Connect, RARE-G, RHORCOD, RD-Connect, RD PLATFORM, SPLICE-EB, WHIPPLE'S DISEASE, SARS/FLU-

³⁴ http://bmg.gv.at/home/Schwerpunkte/Krankheiten/Bericht_Seltene_Erkrankungen_in_Oesterreich

³⁵ <http://www.goeg.at/en/Area/National-Coordination-Centre-for-Rare-Diseases-CCRD.html>

³⁶ <https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/aktuelles/aktuelles-seltene-erkrankungen-in-oesterreich.html>

VACCINE and TUB-GENCODEV. Austria is part of the SIOpen-R-NET research network and networks/registries such as ERCUSYN, EUROCAT, IDR, PRINTO, SCNIR and RARECARE.³⁷

E-Rare

Austria was not an official partner in the E-Rare consortium before 2009 and did not participate in the first E-Rare Joint Transnational Call in 2007. The Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund)³⁸ joined the second E-Rare Joint Transnational Call in 2009, and around € 580,000 of funding was granted for Austrian teams participating in 3 projects. Austria participated in the 3rd Joint Transnational Call in 2010/11 and Austrian teams will participate in all together seven of the funded projects. Austria joined the 4th Joint Transnational Call on Rare Diseases Driven by Young Investigators in 2012 and 2 of the 11 projects selected included a team from Austria.

IRDiRC

The Fonds zur Förderung der wissenschaftlichen Forschung as part of the E-Rare group of funders joined the IRDiRC in 2012.

Orphan medicinal products

Orphan medicinal product committee

There is currently no committee for orphan drugs in Austria.

Orphan medicinal product incentives

The Austrian Medicines Law (2001) provides for “the waiving of fees (e.g. for marketing authorisation or variations) for orphan drugs authorised through the national procedure (applicable until 20 November 2005, date from which the centralised route of marketing authorisation of designated orphan medicinal product became mandatory)³⁹”.

Orphan medicinal product market availability situation

As soon as marketing authorisation is provided, orphan medicinal products are available quite quickly in Austria. Actions are foreseen by the National Plan for Rare Diseases in this area (“Recognition of the specificity of rare diseases” and “Improving equal access to established therapies”) to further improve availability.

In 2012 72 orphan medicinal products received an EU market authorisation. The majority of the orphan medicinal products were included in the out-patient reimbursement code (either in the no box or in any of the other categories); only 13 orphan medicinal products were not included in the out-patient reimbursement code. But it is possible that they were used in-patient, i.e. during hospital stay. Only Plenadren is not marketed for sure in Austria.

Table 1. Availability of authorised orphan medicinal products in the Austrian reimbursement code in 2012/2013

Available in out-patient reimbursement code (no box or other categories)		
Active Ingredient	Brand name	Company
Pegvisomant	Somavert	Pfizer
Clofarabin	Evoltra	Genzyme
Imatinib Mesilat	Glivec	Novartis Europharm
Mercaptopurin	Mercaptopurin Nova Labo	Nova Laboratories
Histamin Dihydrochlorid	Ceplene	EpiCept GmbH
Arsentrioxid	Trisenox	Cell Therapeutics (UK)
Tafamidis	Vyndaqel	Pfizer
Aztreonamlysin	Cayston	Gilead
Tobramycin	TOBI Podhaler	Novartis Europharm

³⁷ Based on information provided by the national EU database team PROVISO.

³⁸ <http://www.fwf.ac.at/>

³⁹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p7).

Available in out-patient reimbursement code (no box or other categories)		
Active Ingredient	Brand name	Company
Ofatumumab	Arzerra	GlaxoSmithKline
Nilotinib	Tasigna	Novartis
Dasatinib	Sprycel	Bristol-Myers Squibb
Rilonacept	Rilonacept Regeneron	Regeneron
Ibuprofen	Pedea	Orphan Europe
Trabectedin	Yondelis	Pharma Mar S.A.
Deferasirox	Exjade	Novartis Europharm
Dexrazoxan	Savene	SpePharm
Icatibant	Firazyr	Jerini AG
Betain	Cystadane	Orphan Europe
Carglumsäure	Carbaglu	Orphan Europe
Pirfenidon	Esbriet	InterMune
Romiplostim	Nplate	Amgen
Eltrombopag	Revolade	GlaxoSmithKline
Busulfan	Busilvex	Pierre Fabre
Thiotepa	Tepadina	Adienne S.r.l.
Amifampridin	Firdapse	Eusa Pharma SAS
Sorafenib	Nexavar	Bayer HealthCare
Rufinamid	Inovelon	Eisai
Bosentan	Tracleer (Ftbl)	Actelion Registration
Iloprost	Ventavis	Schering AG
Sildenafil	Revatio (Ftbl)	Pfizer
Ambrisentan	Volibris	GlaxoSmithKline
Nelarabin	Atriance	GlaxoSmithKline
5-Aminolaevulinsäure	Gliolan	Medac
Plerixafor	Mozobil	Genzyme
Miglustat	Zavesca	Actelion Registration
Velaglucerase alfa	VPRIV (1 ST)	Shire
Alglucosidase alfa	Myozyme	Genzyme Europe
Zinkacetat Dihydrat	Wilzin	Orphan Europe
Laronidase	Aldurazyme	Genzyme Europe
Idursulfase	Elaprase	Shire
Lenalidomid	Revlimid	Celgene Corporation
Thalidomid	Thalidomide	Celgene Corporation
Azacitidin	Vidaza	Celgene Corporation
Mitotan	Lysodren	Laboratoire HRA
Temsirolimus	Torisel	Wyeth
Cladribin	Litak	Lipomed
Mifamurtid	Mepact	IDM Pharma
Levodopa/Carbidopa	Duodopa Gel	Abbot Products GmbH
Eculizumab	Soliris	Alexion Europe
Sapropterin	Kuvan	Merck Serono
Coffeincitrat	Peyona	Chiesi Farmaceutici

Available in out-patient reimbursement code (no box or other categories)		
Active Ingredient	Brand name	Company
Mecasermin	Increlex	Tercica
Ziconotid	Prialt	Eisai Limited
Everolimus	Votubia	Novartis Europharm
Ruxolitinib	Jakavi (new in 2012)	Novartis Europharm Limited
Decitabine	Dacogen (new in 2012)	Janssen-Cilag
Mannitol	Bronchitol (new in 2012)	Pharmaxis Pharmaceuticals Limited
Pasireotide	Signifor (new in 2012)	Novartis
Not available in the out-patient reimbursement code		
Active Ingredient	Brand name	Company
Anagrelid-Hydrochlorid	Xagrid	Shire
Nitisinon	Orfadin	Swedish Orphan
Hydroxycarbamid	Siklos	Addmedica
Porfimer Natrium	Photobarr	Axcan Pharma
Hydrocortison	Plenadren	Duocort Pharma
Galsulfase	Naglayzme	BioMarin
Stiripentol	Diacomit	Laboratoires Biocodex
Alipogene tiparvovec	Glybera (new in 2012)	uniQure biopharma B.V.
Teduglutide	Revestive (new in 2012)	Nycomed
Mercaptopurine	Xaluprine (new in 2012)	Nova Laboratories Limited
Brentuximab vedotin	Adcetris (new in 2012)	Seattle Genetics UK Limited
Ivacaftor	Kalydeco (new in 2012)	Vertex Pharmaceuticals (U.K.) Limited
Concentrate of proteolytic enzymes enriched in bromelain	NexoBrid (new in 2012)	Teva Pharma GmbH

Source: Austrian PPI service 2013

Orphan medicinal product pricing policy

In case a marketing authorisation holder applies for reimbursement at the Austrian Social Insurance in case of out-patient treatment, i.e. inclusion in the positive list / Austrian Reimbursement Code (Erstattungskodex, EKO), the product falls under statutory price regulations. Thus, its maximum ex-factory price may not exceed the EU-24 average price. The final decision on the reimbursement price is made by the Association of Austrian Social Security Institutions after negotiations with the company. The way of the application and the decision process is regulated according to specific principles called VO-EKO in German. In case the orphan medicinal product is not reimbursed, its price may be determined by the manufacturer alone.

The Austrian Social Insurance Fund reported to have received 14 submissions for orphan drugs between 2006 and 2011, whereby:

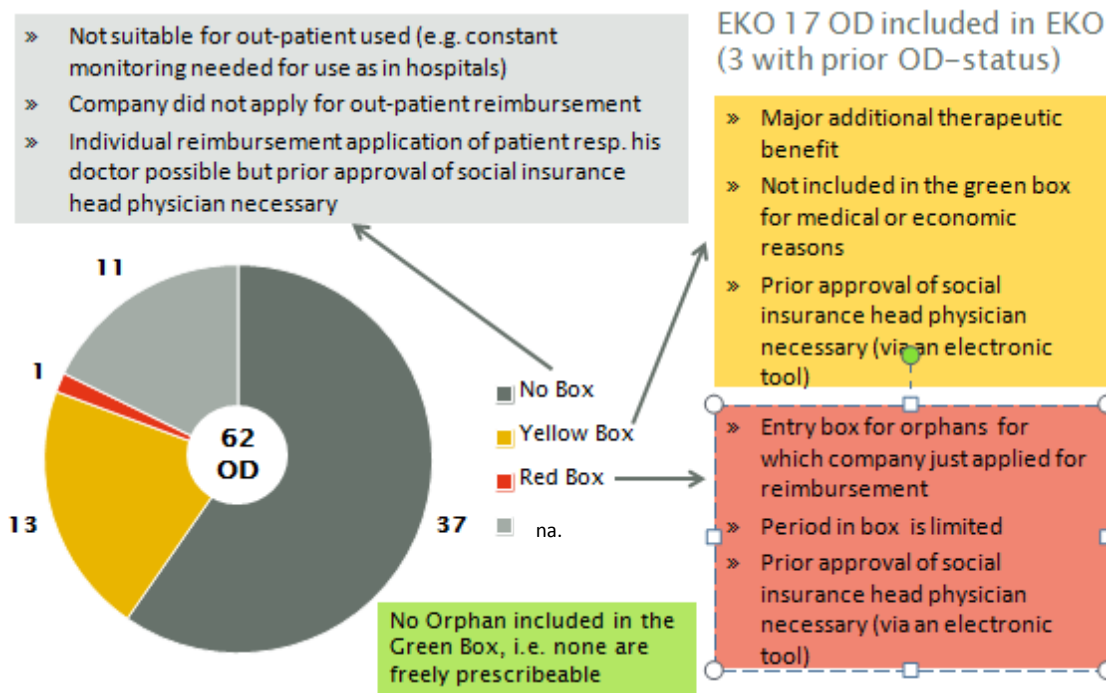
- 2 submissions included 1 clinical trial
- 7 submissions included 2 clinical trials
- 5 submissions included 3 clinical trials (maximum allowed)
- All but one submissions included at least 1 Randomised Clinical Trial
- In half of the submissions placebo was used as the only comparator, although therapeutic options were available

Unauthorised orphan medicinal products may be imported on case-by-case decisions, but in general compassionate use of orphan medicinal products is not allowed. The vast majority of orphan drugs are dispensed in hospitals.

Orphan medicinal product reimbursement policy

According to the Austrian Social Insurance Law (ASVG) insured patients must be granted all necessary forms of medical treatment in a sufficient and appropriate way as long as adequacy of resources used is reasonable⁴⁰. Contract physicians are entitled to prescribe all medicines included in the Austrian Reimbursement Code (EKO)⁴¹ - considering specific rules (e.g. second-line therapy) - on behalf of the sickness funds (general reimbursement). Specific medicines require ex-ante or ex-post approval of a head physician (“Chefarzt”) of the contracting sickness fund. The same is true for exceptional cases where a pharmaceutical is not listed in the Reimbursement Code. To obtain the approval the prescribing physician needs to send a written request to the sickness fund via an electronic online tool. Decisions of the sickness fund’s head physicians depend on medicinal and pharmacological necessities as well as economic criteria. In practice, orphan medicines usually belong to a group requiring prior approval, see Figure 2 below.

Figure 2: Out-patient reimbursement status of all authorised orphan medicinal products with an active orphan designation in Austria, 2012⁴²



If it is determined that a medicine is best applied in a hospital setting, e.g. because of the complexities of administration (as it is for instance the case for “Elaprased”, a drug for an enzyme replacement therapy), then there is no need for reimbursement in the outpatient setting. In exceptional cases, reimbursement may be still approved, however, if the administration is done on an outpatient basis and this is medically justified. For orphan medicinal products not included in the reimbursement code (EKO), the attending physician may still seek approval from the sickness fund (e.g. requesting administration of the orphan drug as out-patient treatment).

In case a patient is seeking to obtain approval for treatment outside of Austria, the same procedure as described above applies (i.e. ex-ante approval by the head physician). In the last four years no treatment with orphan drugs taking place outside of Austria has been approved, however, several patients underwent diagnostic testing in other countries, e.g. in Germany.

Interviewed national experts explained to the CCRD team that patients could experience delays in the reimbursement of orphan medicinal products due to fragmented funding responsibilities. The public payer of medicines in Austria depends on the place of treatment, i.e. the owners of hospitals having to pay for intramural care whereas the regional sickness funds cover medicines prescribed in out-patient care. Sickness funds pay a lump-sum for the provision of in-patient care for their insured to the regional hospital funds.

⁴⁰ Art. 133 ASVG 1955, regulating the extent of medical treatment [Art. 133 ASVG 1995; BGBl. No. 189/1955]

⁴¹ Art. 31.3(12) ASVG, on the publication of the Reimbursement Code EKO (Art. 31.3(12))

⁴² CCRD 2013 based on EKO 1/2013 and Warenverzeichnis 1/2013.

In 2012 public expenditure per prescription for orphan drugs amounted to around €2,700. Altogether the Austrian Social Insurance spent € 106.5 million on orphan drugs in 2012, and €93.2 million in 2011⁴³. In 2011 3.5% of all pharmaceutical expenditure was caused by orphan medicinal products where as expressed by number of prescriptions the share was only 0.03%.

Table 2: Expenditure of Austrian Social Insurance for medicines and orphan drugs used out-patient, 2011 and 2012⁴⁴

Indicators	2011	2012
Expenditure		
Total PE by Social Insurance	€ 2 654 205 566	-
Social Insurance Expenditure for Orphan Drugs*	€ 93 173 418	€ 106 471 427
OD share on Total PE	3.5%	-
Medicines Prescriptions		
Total number of prescriptions	120 348 529	-
No. Of OD-prescriptions *	34 522	39 322
OD share on total number of prescriptions	0.03%	-
Ø Cost per prescription		
All medicines	€ 22.05	
Orphan Drugs *	€2,700	

PE = Pharmaceutical Expenditure, OD = Orphan Drug

Other initiatives to improve access to orphan medicinal products

Any kind of off-label use is not well accepted by public authorities in Austria.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

No specific activity reported.

1.2. BELGIUM

Definition of a rare disease

Stakeholders in Belgium define rare diseases as life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. As a guide, low prevalence is taken as prevalence of less than 5 per 10 000 individuals in the European Community.

National plan/strategy for rare diseases and related actions

In addition to the Belgian Cancer Plan (since 2008), the Minister of Social Affairs and Public Health has developed a National Plan for Chronic Illness with five priorities: (1) the recognition of a statute for persons with a chronic disease; (2) the creation of an observatory for chronic illness; (3) to increase the quality of life of persons with a chronic illness by simplification of the healthcare and social security administration; (4) the social inclusion of persons with a chronic illness both in the work situation as in the society in general and finally (5) to ensure the access and the financial affordability to adequate health care in the broad sense of the word for persons with a chronic illness.

During the development of this plan, the awareness of the specificities of the needs of patients with rare diseases grew and as a consequence the need to develop specific measures for Rare Diseases became apparent.

A request was made by the Fund for Rare Diseases and Orphan Drugs to the Belgian Minister of Health and Social Affairs, on 12 December 2008 for political and financial support to the Fund so as to advance the

⁴³ See table 2.

⁴⁴ Note: All medicines expenses below the prescription fee (around € 5,-) are not included in these figures. Source: Austrian Social Insurance 2013 (Maschinelle Heilmittelabrechnung).

development of a proposition for a Belgian Plan for Rare Diseases. In February 2009, the Belgian House of Representatives adopted a resolution for a plan of action for rare diseases and orphan medicinal products. The Fund for Rare Diseases and Orphan Drugs, managed by the King Baudouin Foundation, has been financially supported for two years (2009-2011) within the framework of the Belgian Plan for Chronic Diseases to develop a proposition of a Belgian Plan for Rare Diseases. An additional request was made for financial support for the umbrella patient association "Rare Diseases Organisation Belgium" (RaDiOrg).

Patient representatives, physicians and other specialists, paramedical staff, insurance organisms, social service representatives, members of industry, the Orphanet Belgium team and administration participated in the working groups of the Fund for Rare Diseases and Orphan Drugs that have developed a set of recommendations grouping specific measures into different domains. The development of these recommendations was elaborated in two phases:

- Phase 1 concerns recommendations elaborated in 2010 for the following four central topics: (1) diagnostics and treatment; (2) codification and inventory; (3) information, awareness and patient empowerment; and (4) access and cost.
- Phase 2 concerns recommendations elaborated in 2011 for the following topics: non-medical costs of rare diseases; international networking, research, adherence; advanced therapy medicinal products, ethical issues, teaching and education, including therapeutic education and finally clinical trials.

The final set of proposals consisting of the updated recommendations of phase 1 integrated with the recommendations of phase 2 was sent to the minister of Social Affairs and Public Health at the end of the first semester of 2011. This report is available online on the website of the King Baudouin Foundation in English, French, German and Dutch languages⁴⁵. The proposed plan consists of 42 recommendations and measures that can be grouped into five central themes: Expertise and multidisciplinary; Collaboration and networking; Knowledge, information and awareness; Equity in access; and Governance and sustainability."

A steering committee appointed by the Minister of Public Health is now in place which will analyse the proposals in terms of financing and the existing plans for cancer and chronic diseases.

Most of the expenditures for rare diseases are covered by the general health system budget. A Special Solidarity Fund is also in place which can be used for patients whose costs are not covered by the health care system (for example some Orphan medicinal product costs). In addition a small specific budget is allocated specially for rare diseases.

Centres of expertise

In Belgium there are several centres specialised in one rare disease or a group of rare diseases. Some of these centres are recognised by the National Institute for Health and Disability (NIHDI) and work under a convention. These centres include: cystic fibrosis centres, and the centres for metabolic diseases and neuromuscular diseases.

An additional budget of €2 million is allocated for the development and the strengthening of these types of multidisciplinary centres of expertise. A group of experts have developed a tool for prioritisation and the working modalities of the centres of expertise in order to implement this action.

On the other hand, genetic counselling, carried out by a multidisciplinary team, will be financed through a new convention with the 8 Belgian genetics centres. The convention also includes guarantees for the adequate quality control and registration of clinical activities. The Belgian Centres for Human Genetics have a full service offering different types of tests and technologies, and patient and family counseling.

Registries

Nationally funded patient registries exist for cystic fibrosis and a set of neuromuscular diseases, and collect extensive data. In the recommendations of the King Baudouin Fund further financing of these registries is proposed. At the moment there are no designation procedures in place for other rare disease-specific registries. Belgian clinicians also contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, EIMD, ENRAH, EUROGLYCANET, EUNEFRON and EURECHINOREG.

As epidemiological data on Belgian rare disease patients is very scarce and fragmented and as this information is essential for health care planning and monitoring a conceptual note was written concerning the creation of a Central Registry of Rare Diseases able to collect a small set of basic variables on rare disease patients. The conceptual note, approved by a group of stakeholders was accepted in December 2011 and a

⁴⁵ <http://www.kbs-frb.be/publication.aspx?id=271066&LangType=2060>

⁴⁶ <http://www.kbs-frb.be/publication.aspx?id=288128&LangType=1033>

budget was allocated for 2012-2013 to the Scientific Institute of Public Health for creation of a Central Registry for Rare Diseases. Objectives for this time period are the mapping of expertise in rare diseases in Belgian hospitals including further mapping and characterisation of rare disease patient databases, defining criteria for prioritisation in elaborating new disease-specific registries, participation in EPIRARE, defining the common data set and developing a business plan and privacy plan for a central registry.

Neonatal screening policy

Neonatal screening in Belgium is a regional competency and is organised by the Vlaams Agentschap Zorg en Gezondheid (Flemish Community) and La Direction générale de la santé du Ministère de la Communauté française (French Community). The program in Flanders encompasses screening for following 11 metabolic diseases: phenylketonuria/hyperphenylalaninemia, congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, medium-chain acyl-CoA dehydrogenase deficiency (MCAD), multiple acyl-CoA dehydrogenase deficiency (MADD), glutaric acidemia type I, isovaleric acidemia, maple syrup urine disease (leucinosis), propionic acidemia and methylmalonic acidemia. In the French community neonatal screening is provided for 6 metabolic diseases: phenylketonuria, congenital hypothyroidism, maple syrup urine disease (leucinosis), galactosaemia, tyrosinemia and homocystinuria. In addition, a specific screening for the risk group for thalassemia is organised by the Brussels Capital Region.

Genetic testing

Genetic testing is carried out exclusively by 8 Centres for Human Genetics, whose operational standards are established by Royal Decree and reimbursed by the NIHDI.

All genetic centres have or are in the process of obtaining an accreditation of their diagnostic activities. An accreditation of the laboratories will be obligatory by January 2014. There are no officially recognised reference laboratories, however the genetic centres cooperate intensively and exchange patient samples for genetic testing based on the expertise of the different laboratories on an informal basis. National guidelines for genetic testing, genetic counseling and clinical management are available for some diseases and are being developed within the College of Human Genetics in cooperation with the scientific organisation of the geneticists, the Belgian Society for Human Genetics.

The reimbursement conditions of genetic tests are currently being revised. The new nomenclature offers a stratified reimbursement system and includes a comprehensive list of diagnoses and genes for which testing is available in Belgium.

Genetic testing abroad is possible, when referred by the Belgian genetic centres: the genetic centres send the samples to a foreign reference laboratory. The genetic tests carried out abroad will be reimbursed by convention with the 8 Belgian genetic centres. A list of authorised tests and the foreign reference laboratories is in preparation: this initiative is part of a decree for the creation of a convention between the NIHDI and the genetic centres that is in force since 1 January 2013.

Diagnostic tests are registered as available in Belgium for 401 genes and an estimated 478 diseases in the Orphanet database⁴⁷.

National alliances of patient organisations and patient representation

Rare Diseases Organisation Belgium (RaDiOrg.be) is a non-profit organisation established in January 2008. RaDiOrg.be regroups around 49 patient organisations for rare diseases in Belgium and is affiliated with EURORDIS. All these organisations are members of the general council of RaDiOrg.be. RaDiOrg.be activities include the organisation of the Rare Disease Day, information and training for patient organisations as well as their needs towards public authorities. RaDiOrg.be is funded by the Federal Government and the Belgian pharmaceutical industry umbrella group Pharma.be.

Patients are well represented in meetings concerning the rare disease situation in Belgium: RaDiOrg.be and two other patient organisation platforms (VPP and LUSS) are recognised representatives of patients in the Fund. In addition, it was decided by law (11 February 2010) that an observatory on chronic diseases will be created including patient organisation representatives and health insurance representatives in order to advise the NIHDI on all issues concerning accessibility of care for chronically ill people, including rare disease patients. The mission of the observatory on chronic diseases is to create awareness of the existing everyday problems of people with a chronic illness and to formulate recommendations and solutions in order to address these needs. This observatory consists of two taskforces: a scientific taskforce and a consultative taskforce.

⁴⁷ Information extracted from the Orphanet database in December 2012.

Sources of information on rare diseases and national help lines

Orphanet activities in Belgium

From 2001 onwards there is a dedicated Orphanet team in Belgium. In the past the team was hosted by the Centre of Human Genetics at the Catholic University of Leuven. As of April 2011, the start of the Orphanet Joint Action, a team for Belgium has been designated at the Scientific Institute for Public Health (IPH) by the Federal Public Service for Public Health, Food Chain Safety and Environment. The Federal Public Service of Public Health itself will also participate in the Orphanet project from April 2011 onwards. The team published the Orphanet Belgium national web page in 2012. The team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The NIHDI provides further support for the Orphanet team at the institute as to carry out the Dutch translation of Orphanet content in order to increase the linguistic accessibility for Belgium's population. Scientific board meetings for the Belgian Orphanet site started in 2008 to validate the data already gathered on the existing rare disease services and research activities in Belgium. Currently the validation procedure is being revised. For most activities the validation procedure has been revised by the coordinating board. Inclusion criteria and the registration procedure are published on the country Orphanet site.

Official information centre for rare diseases

There is no official information centre or website on rare diseases other than Orphanet.

Help line

There is currently no rare diseases help line in Belgium.

Other sources of information

RaDiOrg.be maintains an informative website (www.radiorg.be) which publishes information on rare diseases and patient groups in Belgium: RaDiOrg is also since 2012 present on Facebook. The websites www.weesziekten.be and www.maladiesrares.be provide additional information on the actions of the Fund for Rare Diseases and Orphan Drugs, in both French and Dutch.

The FAMHP (Federal Agency for Medicines and Health Products) contributes to the European database on clinical trials, which became available to the general public in 2011 in line with the transparency position with relation to clinical trials.

Good practice guidelines

Proposals for development of good practice guidelines or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

Training and education initiatives

Proposals for their development or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

National rare disease events in 2012

To mark of Rare Disease Day 2012, RaDiOrg members visited the university hospitals on an awareness raising campaign, providing information about patient organisations and Orphanet. In the context of the finalisation of recommendations for a national strategy for rare diseases, RaDiOrg.be, in collaboration with the Fund for Rare Diseases and Orphan Drugs, organised a national conference on 29 February 2012⁴⁸: the event was dedicated to the recommendations concerning the establishment of centres of expertise and brought together a wide range of stakeholders. During this event, Laurette Onkelinx, Minister of Public Health, received the Edelweiss Award from RaDiOrg for her commitment and support for patients with rare diseases.

Hosted rare disease events in 2012

A number of European events were held in Brussels to mark Rare Disease Day. Eurordis held their annual symposium (entitled 'Rare Diseases a model of EU Solidarity') to mark the day. The event, organised with the European Commission, was held on 29 February 2012, and showcased the successes achieved over the last decade and to discuss the way forward. The European Society of PKU launched their Benchmarking Report, 'Closing the Gaps in Care', on 29 February 2012 in the European Parliament.

⁴⁸ http://www.radiorg.be/sites/default/files/RDD2012-%20report_fr.pdf

Other events announced in *OrphaNews Europe* include: International Childhood Cancer Awareness Day Multistakeholder Meeting (Brussels, 9 February 2012), Rare Cancers Conference: Improving the Methodology of Clinical Research (Brussels, 10 February 2012), Roundtable on Organisation of Rare Cancer Care (Brussels, 12 March 2012), 6th European Conference on Rare Diseases & Orphan Products (Brussels, 23-25 May 2012), 7th European Elastin Meeting (Ghent, 1-4 September 2012), 13th International Workshop on Multiple Endocrine Neoplasia (Liege, 5-8 September 2012), First International Symposium on the Ehlers-Danlos Syndrome (Ghent, 8-11 September 2012), 15th Society for the Study of Behavioural Phenotypes International Research Symposium and Education Day: Social Phenotypes in Genetic Disorders (Leuven, 11-13 October 2012), Epissi Conference on an Optimal European Chronic Care Model: Towards Implementation and Benchmarking (Brussels, 5 December 2012), Symposium ATP1A3 in Disease: From Gene Mutations to New Treatments (Brussels, 10-11 December 2012), European Organisation for Research and Treatment of Cancer (EORTC) 50th Anniversary Conference (Brussels, 15-16 March 2012).

Research activities and E-Rare partnership

National research activities

There are no specific research programmes for rare diseases in Belgium. The FRS-FNRS (Fund for Scientific Research, French-speaking community of Belgium)⁴⁹ and its associated FRSM (Fund for Scientific Medical Research)⁵ provides funding for basic research on rare diseases including rare cancers. Rare disease research also benefits from initiatives such as programmes to stimulate translational R&D. Some fundraising patient organisations also finance rare disease research.

Participation in European research projects

Belgian teams participate, or have participated, in the following a number of European research projects for rare diseases, including: AIP-GENE, ALPHAMAN, ANTIMAL, CONTICANET, CHEARTED, CELL-PID, ESDN, ENRAH, EURAMY, EUREGEN, EUROCARE-CF, EUROSCA, EVI-GENORET, FASTEST-TB, EUNEFRON, EURENOMICS, ESPOIR, EUROSARC, EURO-CDG, EUROAGENTEST 1 AND 2, EUROMOTOR EUROGLYCANET, EURO-SCAR, GENESKIN, GEN2PHEN, GENOMIT, FIGHTHLH, HUE-MAN, KALADRUG-R, LEISHMED, INTREALL, IMPACTT, IMMUNOPRION, MABSOT, MITOTARGET, MYASTAID, NANOTRYP, NEOTIM, NEUROPRION, NEUROMICS, PEROXISOMES, PULMOTENSION, PYRAMID, OCTIPS, OVER MyR, PWS, RATSTREAM, RD PLATFORM, RAREBESTPRACTICES, SIOPEN-R-NET, STEM-HD, TRANSPOSMART, TIRCON, TB-DRUG OLIGOCOLOR and WHIPPLE'S DISEASE.

E-Rare

The FRS-FNRS is a full, contracting member, of the E-Rare and the E-Rare 2 consortium, participating in the decision and implementation process of the network. Although none of the Belgian funding agencies participate in E-Rare's first two Joint Transnational Calls, the Research Foundation Flanders (FWO)⁵⁰ and Fund for Scientific Research (FRS-FNRS) participated in the 3rd Joint Transnational Call in 2011. Belgian teams will participate in four of the 13 funded projects. The FRS-FNRS also participated in the 4th Joint Transnational Call in 2012: a Belgian team will participate in 1 of the 11 projects selected for funding.

IRDiRC

The FNRS and FWO as a member of the E-Rare group of funders joined the IRDiRC in 2012.

Orphan medicinal products⁵¹

Orphan medicinal product committee

The Belgian steering group on orphan diseases and orphan drugs had their first informal meeting in March 2006: this group was composed of representatives from patient organisations, industry, genetic centres, therapeutic centres, hospital pharmacies, the HTA agency, insurance groups, the federal health institution and a member of parliament. The steering group organised a national symposium^{52,53} on orphan medicinal products in November 2006. The steering group has gone on to develop a strategy to increase awareness in Belgium concerning the problems rare diseases present and the reimbursement of orphan medicinal products. In December 2007, the steering committee was officially integrated into the "Fund for Rare Diseases and Orphan

⁴⁹ www.frs-fnrs.be

⁵⁰ www.fwo.be

⁵¹ This section has been written with information from the section on Belgium in the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (pp35-45).

⁵² <http://www.weesziekten.be/symposiumfr.htm>

⁵³ <http://www.maladiesrares.be/symposiumfr.htm>

Drugs" in the King Baudouin Foundation of Belgium. At the end of 2008, ad hoc working parties were created by this committee to address the issues related to orphan medicinal products and rare diseases and to develop strategic solutions.

Orphan medicinal product incentives

Since 2006, at the initiative of the NIHDI, the revenues of orphan medicinal products are no longer subject to so called 'pharmaceutical taxes' (i.e. taxes, earmarked for social security), on sales of reimbursable drugs.

Orphan medicinal product market availability situation

Since 2001, orphan medicinal products obtain Marketing Authorisation (MA) through the centralised procedure at the EMA. In addition orphan status can also be attributed by AFMPS (National Procedure) ex: Flolan, Duodopa. As for the list of the reimbursed orphan medicinal products, please see the section "Orphan medicinal product reimbursement policy". The products that are not reimbursed can be nonetheless available on the market and this is the case for Wilzin and Pedeia, which are included in the list of CBIP.

Other initiatives to improve access to orphan medicinal products

The Law of 1 May 2006 provides for Compassionate Use programs (in case of a medicinal product without a MA in Belgium), or Medical Need programs (in case of a medicinal product with a MA in Belgium but for another indication)⁵⁴. A last possibility for non-reimbursed pharmaceutical products is reimbursement by the Special Solidarity Fund (SSF), which is regulated by the Law of 14 July 1994, Articles 24 and 25. Conditions for compassionate use or reimbursement through the SSF are defined by law. In 2007, orphan medicinal products accounted for about 35% of the SSF's total budget⁵⁵.

Orphan medicinal product pricing policy

The Minister for Economic Affairs determines the maximum manufacturer selling price of reimbursed prescription medicines, taking advice from the Ministry's Medicines Pricing Commission. The agreed price is forwarded to the NIHDI for a recommendation to the Minister of Social Affairs and Public Health on reimbursement. The actual purchase price of medicines used in hospitals are based on negotiations between manufacturers and the hospitals⁵⁶.

Orphan medicinal product reimbursement policy

According to information collected for the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, "in Belgium, one of the most important measures has been the adoption of the Royal Decree of 8 July 2004 on the reimbursement of orphan medicinal products. This Decree, which entered into force on 20 July 2004, created a 'Committee of Doctors for Orphan Medicinal Products' within the Healthcare service of the NIHDI, the body responsible for issuing opinions on orphan medicinal products when an opinion is required, including with regard to evaluating individual rights to reimbursement. It also evaluates the existing reimbursement conditions for these products and draws up an annual activity report"⁵⁷.

Drug reimbursement decisions are taken by the Minister of Social Affairs, after advice from the Drug Reimbursement Committee (DRC) as well as the Minister of Finances and the agreement of the Minister of the Budget. Orphan medicinal products follow the same procedure as Class I pharmaceutical products, i.e. products for which the company claims a therapeutic added value. However, unlike for Class I pharmaceutical products, no pharmaco-economic evaluation has to be submitted for orphan medicinal products. A decision on the reimbursement is taken within 180 days following the submission of the reimbursement request.

At the end of December 2011, 50 orphan medicinal products were eligible for reimbursement in Belgium (including two products that do not have EMA orphan medicinal product status, but that are reimbursed for an orphan indication) for a total of 57 orphan indications⁵⁸. Orphan medicinal products are most of the time fully reimbursed (except Tracleer in the prevention of digital ulcers in sclerodermia); although for some of them reimbursement depends on prescription by specialists belonging to a recognised centre that provides treatment.

⁵⁴ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p40).

⁵⁵ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp35-45).

⁵⁶ Orphan Drugs in Europe : Pricing, reimbursement, Funding and Market Access Issues (2011 Edition), Donald Macarthur, (p 99).

⁵⁷ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p8).

⁵⁸ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p39).

The list of medicinal products, including those which have in the past the label of orphan drugs, reimbursed by the NIHDI⁵⁹ includes: Afinitor, Aldurazyme, Atriance, Benefix, Busilvex, Carbaglu, Casyston, Cerezyme, Cystadane, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Flolan, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kogenate, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Normosang, Nplate, Orfadin, Refacto AF, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tassigna, Thalidomide, Thelin, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Vpriv, Xagrid, Xyrem, Yondelis, Zavesca⁶⁰.

In normal circumstances, the specialist first obtains the approval of a Medical Advisor of the patient's sickness fund to prescribe the medicine. The Medical Advisor is able, but is not obliged to, request the advice of a "College of Medical Doctors for Orphan Drugs" (CMDOD). In practice, all sickness funds have agreed to refer all requests to the CMDOD if one exists. Separate Colleges exist for separate products and the DRC decides whether or not a College is established. At the end of 2012, there were 31 colleges for 59 orphan medicinal products. Individual reimbursement decisions are made on a case by case by the Medical Advisor based on the advice of the CMDOD. They are valid for periods going from 6 to 12 months⁶¹ and can be renewed.

A study entitled "Policies for Orphan Diseases and Orphan Drugs⁶²", compiled by the Belgian Health Care Knowledge Centre, was published in June 2009. This is a comprehensive English-language report that compares the Belgian orphan medicinal product reimbursement policy with other countries, estimates the current budget impact of orphan medicinal products, forecasts the expected future budget impact, and offers recommendations for policy makers concerning orphan medicinal products.

In 2012 an article⁶³ was published, assessing the system of reimbursement for orphan drugs in Belgium, outlining the official criteria by which reimbursement decisions are achieved: therapeutic value, price, proposed reimbursement tariff, clinical value and budget impact, as well as other negotiable factors including price adjustments, employment incentives for manufacturers, diagnostic test funding by the company, and patient population restrictions. While reimbursement approval is granted to the majority of orphan drugs in the country, the authors identify measures to improve the system, such as good practice principles for analysing budget-impact, further standardisation of applications for reimbursement, and enhanced European cooperation in sharing clinical evidence.

Orphan medicinal product study

The study *Budget impact analysis of orphan drugs in Belgium: estimates from 2008 to 2013*, appeared in the May 2010 issue of the *Journal of Medical Economics*⁶⁴ and is the first study of its kind to measure the impact of orphan medicinal product expenditures on a country's overall medicinal product budget. Determining the total orphan medicinal product costs in Belgium in 2008, the authors then forecast the impact over the next five years. Using multiple sources, the authors calculate that orphan medicinal product expenditures (€66.2 million) comprised 5% of the country's total hospital drug budget in 2008 and that the impact "is substantial and rising, thereby putting pressure on total drug expenditure in coming years". The increase can be attributed to the growing number of orphan medicinal products receiving marketing authorisation in the EU. To estimate the future impact, the study contemplated three scenarios "reflecting different levels of growth in the number of drugs that gain marketing authorisation in the European Union, the number of drugs that gain reimbursement in Belgium, and the average annual cost per patient per drug in Belgium". The study can be instructive to other European countries trying to determine the impact of orphan medicinal products on their health budgets. The second, French language article, appearing in the "Journal de Pharmacie de Belgique" takes a look at the policies governing orphan medicinal product development and authorisation. The authors call for the creation of European-level registries in order to follow the evolution of rare diseases as well as the "efficacy of orphan medicines, the majority of which are relatively expensive". The authors also recommend a mechanism for evaluating reimbursement requests, in order to "ensure a coherent application of reimbursement criteria". The authors compare specific practices amongst European countries – particularly Belgium, France, Sweden, the United Kingdom and Italy. Italy, for example, requires a patient to enrol in a national registry prior to dispensing a particular orphan product. Many countries (with the exception of Sweden and the UK) look to their neighbours when it comes to determining a price for a specific product. The authors assert that this practice leads sponsors to seek distribution first in those countries where obtaining the desired price is easier.

⁵⁹ http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/OrphanCns.asp (updated 01/04/2010)

⁶⁰ Please note that for Afinitor, Sutent and Xyrem, the orphan designation was withdrawn.

⁶¹ *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp43-44).

⁶² Link to the report: http://www.kce.fgov.be/index_en.aspx?SGREF=5211&CREF=13651

⁶³ <http://www.ncbi.nlm.nih.gov/pubmed/21905759>

⁶⁴ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=20482245

For Belgium, the authors recommend establishing a “unique counter” within the social security agency that would centralise all reimbursement requests and could oversee a standardised registry system similar to that used in Italy.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Facilities for respite care and therapeutic recreational programmes are under investigation but do not currently exist in a structured fashion for rare diseases. A budget is foreseen in the framework of the Chronic Disease Programme for the financing of respite care structures for children with chronic diseases, including rare diseases patients. Three projects are currently being developed and have started in 2011. Governmental measures for the integration of handicapped persons already exist in Belgium by means of social and financial support.

1.3. BULGARIA

Definition of a rare disease

Stakeholders in Bulgaria accept the definition of a prevalence of no more than 5 in 10 000 individuals. This definition is officially mentioned in the Bulgarian National Plan for Rare Diseases.

National plan/strategy for rare diseases and related actions

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013). The Bulgarian National Plan for Rare Diseases started on 1 January 2009 and will last for 5 years. Bulgaria’s National Plan for Rare Diseases is currently active and consists of nine priorities targeting all rare diseases:

- Collection of epidemiological data for rare diseases in Bulgaria by creation of a national register;
- Improvement of the prevention of genetic rare diseases by enlarging the current screening programmes;
- Improvement of the prevention and diagnostics of genetic rare diseases by introducing new genetic tests, decentralisation of the laboratory activities and easier access to medico-genetic counselling;
- Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families;
- Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases;
- Feasibility study on the necessity, possibility and criteria for the creation of a reference centre for rare diseases of functional type;
- Organisation of a national campaign to inform society about rare diseases and their prevention;
- Support and collaboration with NGOs and patient associations for rare diseases;
- Collaboration with the other EU members.

A National Consulting Council on Rare Diseases (NCCRD) has been established by the Ministry of Health, to supervise the progress and implementation of the plan. NCCRD includes medical professionals, Ministerial representatives and a representative of the National Alliance of People with Rare Diseases. Although the estimated budget of the Plan is €11.3 million, the assigned funds are much less and are disproportionately distributed (i.e. directed almost exclusively towards genetic testing and screening activities). The estimated budget does not take into account the costs for the provision of clinical services for rare disease patients. Funding for rare disease policies is provided by the Ministry of Health and reimbursements of drugs for rare diseases are covered by the National Health Insurance Fund (defined by Ministerial Ordinance 38). Since 2011 there has been a tendency to gradually transfer all rare diseases treatment coverage from the Ministry of

Health to National Health Insurance Fund. However, the Ministry of Health stays a major actor in rare diseases treatment provision through the Ministry of Health-operated Fund for Children's Treatment and Commission for Treatment Abroad.

The National Plan's implementation was greatly disrupted by the country's general economic difficulties and pending healthcare reforms. Nevertheless, individual efforts from medical professionals, university clinics, patient groups and association have greatly contributed for the overall progress of rare diseases issues in Bulgaria. Many new rare diseases activities have been launched by different stakeholders, an excellent rare disease network has been established within the country and rare diseases awareness has been significantly improved. Funded by the National Plan, national newborn screening programmes have been stabilised and improved, which has positively affected the start age of therapy in newborns picked up by mass and selective screening programs, diagnosis and therapy have also moved forward. There is now more mutual confidence and close collaboration among different groups, as well as more active "crosstalk" regarding rare diseases policy (especially rare diseases centres of expertise).

In addition to these measures, the First National Conference for Rare Diseases in Bulgaria (28 to 30 May 2010)⁶⁵, organised within the scope of the EUROPLAN project, brought together stakeholders in order to discuss the provisions of the plan and its implementation. The conference participants agreed on the following general proposals and guidelines for actions at national level: to fully support of the priorities set out in the EU Council Recommendation on an action in the field of rare diseases adopted on 8 June 2009; to secure the implementation of the Bulgarian National Programme for rare diseases with the appropriate funds as defined in the budget framework; to stress the need for urgent legislative initiatives to protect the rights of people with rare diseases and to ensure the adequate prevention, treatment, rehabilitation and social cares; to encourage the establishment of epidemiological registries for rare diseases in Bulgaria; to implement of an integrated approach to people with rare diseases and their families; to organise a public campaign to fund and stimulate research on rare diseases in Bulgaria. The final report of the workshop has been published and is available online for public consultation⁶⁶. Annual rare disease conferences continue to be organised so as to discuss with stakeholders the provisions and advancements of the national plan.

Two major developments concerning the NCCRD and the Bulgarian National Plan took place in 2012. The first one was the Annual National conference for rare diseases⁶⁷ in September 2012, which gathered more than 160 national rare diseases stakeholders to discuss the official designation of rare diseases centres of expertise in Bulgaria. The participation of the Chair of Committee on Healthcare at the Bulgarian Parliament (Dr. Daniela Daritkova), the Director of the National Health Insurance Fund (Dr. Plamen Tsekov) and leading experts from the Ministry of Health was an encouraging sign for all local rare diseases stakeholders. The second one was that NCCRD board was significantly renewed at the beginning of 2013. Its members are now supposed to take more active role in the EU Cross-Border Healthcare Directive transposition in Bulgaria, especially on the matter of rare diseases and centres of expertise.

Centres of expertise

Currently, there is no official designation procedure for centres of expertise for rare diseases in Bulgaria. The national plan was supposed to carry out a feasibility study on the necessity, possibility and criteria for the creation of a centre of expertise for rare diseases. However, by the end 2012 no such steps have been undertaken.

Nevertheless, there are several academic centres that are specialised as centres of research, treatment and management for rare diseases, i.e. cystic fibrosis, mucopolysaccharidosis, thalassemia major, Gaucher disease and neuromuscular diseases. Treatment with orphan medicinal products is currently reimbursed in these centres, which also manage the provision of very expensive orphan medicinal products. Medical experts from these centres also participate in developing protocols for the National Health Insurance Fund, which serve the treatment of rare disease patients.

Rare diseases centres of expertise for rare diseases were the principle focus of the Bulgarian Third National Conference for Rare Diseases and Orphan Drugs (14-15 September 2012): a panel of experts focused on the EUCERD quality criteria for centres of expertise for rare diseases, with the goal of adopting a set of designation criteria that could be proposed to the Ministry of Health. Given the wide range of rare diseases and problems associated with them, stakeholders agreed that it is difficult to approach uniformly all these issues.

⁶⁵ <http://www.conf2010.raredis.org/>

⁶⁶ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Bulgaria_n%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

⁶⁷ Brief report of the 3rd National Conference for Rare Diseases and stakeholders feedback in "Rare Diseases & Orphan Drugs" (October 2012, in both Bulgarian and English) http://raredis.org/pub/Newsletter/Newsletter_12_EN.pdf

However, requirements such as multidisciplinary, recognised expertise and reputation, networking with other similar national and European structures, cooperation with patient organisations were unanimously supported as criteria for designation of these centres. On the other hand, not all Bulgarian experts believe that the criteria for scientific contribution and participation in clinical trials can be fully met, mainly due to the insufficient human and material resources for these activities in the hospitals here.

In addition to these measures, since May 2009, the Bulgarian Association for Promotion of Education and Science runs highly specialised medical centre for rehabilitation and education of people with rare diseases "RareDis". The main idea is to upgrade the services of the Information Centre for Rare Diseases and Orphan Drugs, by launching a tertiary-level rehabilitation centre, aimed at improving the quality of life of people with rare diseases.

Registries

The first priority in the National Plan was to provide epidemiological data on rare diseases in Bulgaria through the establishment of a National Registry. The arrangements for the establishment and operation of the registry are within the competence of the Programme's National Consulting Council for Rare Diseases (NCCRD) within the Ministry of Health. The registry's tasks include:

- Collecting, summarising, and providing epidemiologic information on the incidence and prevalence of rare diseases in Bulgaria;
- Assisting the preparation of diagnostic and therapeutic protocols and standards for treatment of rare diseases;
- Assisting the Ministry of Health, the Ministry of Labour and Social Policy, and the National Health Insurance Fund in the planning and delivery of expensive treatment and medical care to patients with rare diseases;
- Improving the interaction between health services and patient organisations;
- Providing and publishing data needed for planning and comparison on a regional and national level.

However, the National Registry has still not been established. Still, rare disease stakeholders realise the importance and benefits of registry tools and several registries show the fruit of collaborative efforts. The Bulgarian Second National Conference for Rare Diseases and Orphan Drugs in 2011 was an opportunity to present and discuss these issues. The forum demonstrated a growing interest and motivation for the establishment and implementation of these registries. Consensus was evident among patients and physicians on the need to continue providing support to all the existing epidemiological registries for rare diseases in the country, as an initial step to create the long-expected and so necessary national registry for rare diseases.

By the end 2012 no specific steps for the implementation of this task have been undertaken.

The Bulgarian Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) released a new report⁶⁸ in 2012 listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country. Eight nation-wide epidemiological registries concerning rare diseases have been identified by the ICRDOD: the National registry of Patients with Phenylketonuria, the National Registry of Patients with Primary Immunodeficiencies (PID), the National Registry of Patients with Thalassemia Major, the National Registry of Chronic Myeloid Leukaemia Patients, the National Registry of Crohn Disease Patients, the National Registry of Wilson Disease Patients, the National Registry of Gaucher Disease Patients, the National Registry of Mucopolysaccharidosis type 2 Patients. However, this data are not complete and only include registries whose coordinators have provided feedback. The survey will be organised once again in 2013 in order to catch the missing information, as well as the recent developments in this field.

On 28 October 2009, BAPES (Bulgarian Association for the Promotion of Education and Science) was officially given the status of data privacy administrator of rare diseases registries by the Commission for Protection of Data Privacy. Soon after, the collection of epidemiological data for the project "The National registry of thalassaemia major patients in Bulgaria" started. The project is implemented as a result of the common work and cooperation between BAPES, ICRDOD, Medical Centre "RareDis", Bulgarian Scientific Society of Clinical and Transfusion Haematology, university haematology clinics and thalassaemia patient organisations. A subsequent update and collection of new epidemiological data was organised in March-April 2011, results of Phase III were published in June 2011⁶⁹.

⁶⁸ http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf

⁶⁹ http://www.raredis.org/?page_id=2432&mel=4&smel=41&lang=en

Following this very successful model, BAPES has initiated recently 5 new rare diseases registries. In May 2011 the first results from a joint study of BAPES and Wilson disease patient association were published⁷⁰. The Crohn Disease National Registry is already working and its first statistics⁷¹ were officially adopted in June 2011 at a Crohn Disease national workshop. The Bulgarian Scientific Society of Gastroenterology, Gastrointestinal Endoscopy and Abdominal Echography and the university gastroenterology clinics throughout the country have greatly supported and contributed to both Crohn and Wilson patient registries. Just before the Second National Conference for Rare Diseases in September 2011 the provisional results of two new rare diseases patient registries were announced for Gaucher disease and Mucopolysaccharidosis type 2. The corresponding patient associations have provided data, which were analysed by BAPES. In December 2011 BAPES has reached agreements with the Bulgarian Scientific Society for Clinical and Transfusion Haematology and the Bulgarian Scientific Chirurgic Society for launching two new rare diseases registries for primary myelofibrosis and neuroendocrine tumors respectively. In 2012 epidemiological data for the national thalassemia, chronic myeloid leukemia and Crohn disease registries have been updated, as well as pilot epidemiological studies for myelofibrosis and neuroendocrine tumors have been started. A unique character of all BAPES-managed epidemiological registries for rare diseases is that they involve joint activities by all relevant stakeholders.

The Screening Laboratory of the University Pediatric Hospital in Sofia was also created and is currently maintaining several databases, which are primary sources for analysis and evaluation of neonatal screening programmes in Bulgaria. Several modules are implemented (with no government funding): mass neonatal screening registry, primary congenital hypothyroidism, congenital adrenocortical hyperplasia, hyposomatotropism and Turner syndrome patient registries. There were talks with the Ministry of Health to link the Ministry of Health's birth registry with the mass neonatal screening registry and to co-work in real time. All the University Pediatric Hospital registries have proved to be very efficient for the respective rare diseases patients' follow up, as well as medical professional training.

Additionally, some rare tumours are included in the National Cancer Registry, which receives public (governmental) funding.

Bulgaria also contributes to the EURO CARE CF and TREAT-NMD European registries.

Neonatal screening policies

One of the national plan's priorities is to improve the availability and accessibility of the current screening programs. In 1979 mass neonatal screening was introduced in Bulgaria for phenylketonuria, galactosaemia (discontinued in 1993), congenital hypothyroidism and congenital adrenal hyperplasia. Some selective metabolic screening programmes are coordinated by the University Maternity Hospital National Genetic Laboratory in Sofia for the metabolic screening programmes (phenylketonuria), and the University Paediatric Hospital in Sofia for the endocrine screening programmes (congenital hypothyroidism and congenital adrenal hyperplasia). There is logistic coverage of the entire country with more than 130 neonatal structures carrying out blood sampling 3-5 days after birth. Over 90% of neonates are included in existing measures. Ordinance 26 2007 of the Ministry of Health provides equal access to the neonatal screening programmes. However, there exist certain problems, such as postponed mailing of screening cards to centralised labs, and the need for technological upgrades.

The revision and update of the National Medical Genetics Standard (including neonatal screening programmes) started in 2012. It envisages the expansion of the screening panel in accordance with the proposals of screening expert network in Bulgaria. National screening experts even propose to elaborate a separate regulation for neonatal screening, including the designation of the participating laboratories as "centres of expertise" on different sectors (diagnosis, clinical management, consultation, registries, training, etc.). The technological renovation of the centralised screening laboratories, as planned in the National Rare Diseases Plan, has not been carried out yet.

Genetic testing

National guidelines for performance of genetic testing in Bulgaria are regulated by the Health Law and the National Medical Genetics Standard. According to the Health Law (Section IV: Genetic health and genetic testing) genetic testing is performed by accredited genetic laboratories. Genetic tests for the diagnosis of rare disorders are provided mainly by the National Genetic Laboratory (NGL). NGL is a national reference laboratory that provides methodological guidance and control over the activities of the genetic laboratories and performs

⁷⁰ http://www.raredis.org/?page_id=2447&mel=4&smel=44&lang=en

⁷¹ http://www.raredis.org/?page_id=2454&mel=4&smel=43&lang=en

centralised some specialised tests. It was established more than 35 years ago, by initiating of biochemical analysis for some rare disorders and mass neonatal screening for PKU. At the moment NGL provides routine diagnosis with DNA analysis (including prenatal and evaluation of carrier status) for many disorders: cystic fibrosis, phenylketonuria, Wilson disease, neuromuscular disorders, Niemann–Pick (in target population), beta thalassemia, galactokinase deficiency (in target population), microdeletions and microduplications syndromes, inborn hypothyroidism and other. The NGL also has the capacity to perform routine enzymatic analysis and GS/MS analysis for diagnosis of many rare disorders (Krabe, Pompe, MPS). In 2010 the laboratory introduced MS/MS analysis for metabolic study of inherited disorders.

The government organises support of testing by financing diagnostic kits and consumables. Genetic testing abroad is possible for diseases for which the genetic test is not available in Bulgaria, after commission approval. Furthermore, clinical centres, as well as separate research teams have the opportunity through research funded projects by relevant universities and the Ministry of Education's Research Fund to apply for routine implementation of molecular genetic diagnosis for certain rare diseases. In these cases, patients' diagnosis is provided free of charge.

Diagnostic tests are registered as available in Bulgaria for 34 genes and an estimated 85 diseases in the Orphanet database⁷².

National alliances of patient organisations and patient representation

The National Alliance of People with Rare Diseases (NAPRD) in Bulgaria is an umbrella organisation of around 30 rare disease patient associations and single members with rare diseases not represented by an association. It aims to create a link between the people with rare diseases and the representatives of the social and healthcare system. The Alliance works for the right to timely and equal medical care. The organisation also lobbies for the creation of adequate laws in the field of the protection of the rights of the people with rare diseases.

Public funding is available for nation-wide patient organisations in Bulgaria. Patient representatives are members of the management board of the National Health Insurance Fund, the committee for transparency at the Ministry of Health and the national consultative committee on rare diseases.

Sources of information on rare diseases and national help lines

Orphanet activities in Bulgaria

Since 2004 there is a dedicated Orphanet team in Bulgaria, currently hosted by the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD). This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database.

Official information centre for rare diseases

ICRDOD⁷³ is a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES⁷⁴) – a non-government non-profit organisation, registered under the Bulgarian law on non-profit legal in 2003. ICRDOD is a free educational and informative service in Bulgarian and English, providing personalised replies to requests from patients, families and medical professionals. It operates a multilingual website (www.raredis.org) and a rare disease help line - (+359) 32 57 57 97. The ICRDOD also provides a bi-monthly newsletter⁷⁵ ("Rare Diseases & Orphan Drugs"): every issue contains a cover story with an interview, news and announcements and a rare diseases reading list. It is electronic and distributed free of charge. The newsletter is published in two versions – Bulgarian (ISSN 1314-3581) and English (ISSN 1314-359X). The ICRDOD also provides an online registry of rare diseases patients, and a Rare Diseases Library in Bulgarian.

In 2010 ICRDOD started publishing reviews on rare diseases topics. These papers' objective is to summarise important information on particular topics in the field and to present it in a reader-friendly format.

ICRDOD published in September 2012 an updated review of the access to orphan medicinal products for rare diseases in Bulgaria⁷⁶: the report contains 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive drug list and reimbursement; mechanisms for accelerated access to innovative medicines; conclusions. There are 2 annexes, attached to the review: list of orphan medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code,

⁷² Information extracted from the Orphanet database in December 2012.

⁷³ <http://www.raredis.org/>

⁷⁴ http://www.raredis.org/?page_id=2147&mel=8&smel=81&lang=en

⁷⁵ http://www.raredis.org/?page_id=2311&mel=7&smel=71&lang=en

⁷⁶ http://raredis.org/pub/OD_Report_04042011_EN.pdf

active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

The Bulgarian Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) released a new report in 2012⁷⁷ listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country.

The ICRDOD site was substantially renewed and upgraded at the end of 2011. Besides a new look and new layout of content, the site offers several new features for its users, such a subscription for its newsletter

Help line

ICRDOD provides a rare disease help line - (+359) 32 57 57 97 providing personalised replies to requests from patients, families and medical professionals. ICRDOD is a member of EURORDIS-led European Network of Rare Diseases Help Lines and took part in the Network's Caller Profile Analysis 2011 and 2012.

Other sources of information

Departments of Medical Genetics at all University Hospitals and the National Genetic Laboratory also provide information.

Good practice guidelines

Several national best practice guidelines are available in Bulgaria, for example the guidelines prepared, adopted and published by the Bulgarian Cancer Society for oncological diseases, including rare tumours, clinical guidelines for Gaucher disease, neuromuscular diseases, thalassemia.

In 2012, rare diseases experts from the University Pediatric Hospital in Sofia took part in the elaboration of "Growth and Endocrine Disorders in Thalassemia: The International Network of Pediatric Endocrinologists in Thalassemia (I-CET) position statement and guidelines".

Training and education initiatives

The first Eastern European Rare Diseases Summer School⁷⁸ designed for Russian health authorities and legislative institutions was held on 11-18 September 2011. The second edition of this initiative was once again organised in 2012⁷⁹. The Summer School was a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations "Genetics" (Russia) and the Italian National Centre for Rare Diseases (CNMR). The event gave the Russian policy and decision makers an opportunity to learn more about rare disease topics and to understand the significant added-value that rare diseases actions and measures bring to the table. The participants came from a wide range of public fields – federal and regional legislative bodies and health authorities, leading medical institutions, academia, patient organisations and the pharmaceutical industry. The week-long event, which covered a variety of topics including centres of expertise, orphan medicinal products, registries, and national plans, was considered a success by attendees, who reported feeling much better informed on the needs of rare disease patients by the end of the training.

Furthermore, BAPES organises each year a two-day rare disease training seminar for medical students. Medical students have the chance to get acknowledged with the main rare diseases concepts, such definition, major problems, important initiatives, etc. The information and education services, offered by ICRDOD and Orphanet were also presented as high quality and reliable source of information, that medical students could use anytime now during their training or further in their future professional practice. Patient representatives took part in the event too, giving personal testimonials and their own point of view on rare diseases issues.

The Screening Laboratory at the University Paediatric Hospital in Sofia also organises a 3-day training workshop for medical professionals each year.

National rare disease events in 2012

In Bulgaria the Rare Disease Day was celebrated through events in Sofia, Plovdiv, Stara Zagora and Pleven, including a release of balloons in solidarity with rare disease patients in the capital. In Sofia and Varna training sessions were held for general practitioners concerning how to relate to people with rare diseases.

The Third Bulgarian National Conference for Rare Diseases and Orphan Drugs⁸⁰ was held on 14-15 September 2012. 163 participants, including officials from the Parliamentary Health Committee, the Ministry of

⁷⁷ http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf

⁷⁸ http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf

⁷⁹ http://raredis.org/pub/Newsletter/Newsletter_15_EN.pdf

⁸⁰ <http://conf2012.raredis.org/>

Health and the National Health Insurance Fund attended the conference. Centres of expertise for rare diseases were the principle focus: a panel of experts focused on the EUCERD quality criteria for centres of expertise for rare diseases, with the goal of adopting a set of designation criteria that could be proposed to the Ministry of Health. Requirements such as multidisciplinary, recognised expertise and reputation, networking with other similar national and European structures, cooperation with patient organisations were unanimously supported as criteria for designation of these centres. On the other hand, not all experts believed that the criteria for scientific contribution and participation in clinical trials can be fully met, mainly due to the insufficient human and material resources for these activities in the hospitals here. Apart from better care and follow-up of patients, the designation of a medical structure as a centre of expertise for rare diseases will provide new opportunities for the development of the institution, such as increasing knowledge and experience of professionals, and attracting additional external funding through participation in European reference networks and research projects. Logically, both doctors and patients are united behind the need for the status of these centres in Bulgaria to be as fast as possible officialised by the Ministry of Health. A proposal for the development of appropriate regulations will be submitted to the Minister of Health. European and international experience has clearly demonstrated the importance and benefits of such public health institutions: better quality of treatment and care, better organisation of medical services, and more efficient use of funds for rare diseases. The designation of centres of expertise at national level is an important topic considering the steps towards the implementation of the Cross-Border Healthcare Directive.

ICRDOD and NAPRD organised for the first time in Bulgaria a workshop on health technology assessment for rare diseases on 1 November 2012 in Sofia. The event was under the auspices of and hosted by the Healthcare Commission at the 41st National Assembly of Bulgaria. The event aimed to advocate for a better comprehension, access and use of innovative health technologies, including orphan medicinal products.

Many different rare disease-specific training and scientific events were also organised by different stakeholders. For example, several workshops on thalassemia were held (2nd Workshop on thalassaemia major “Multimodal approach in therapy and follow-up”, Summer Academy “Quality of life of patients with β Thalassemia in Bulgaria – focus on endocrine complications”, etc).

Hosted rare disease events in 2012

The Bulgarian Association for Promotion of Education and Science launched and organised in 2005, 2006, 2008 and 2009, the annual “Eastern European Conference on Rare Diseases and Orphan Drugs”. In 2010 for the very first time the event was hosted and co-organised outside Bulgaria, in Saint Petersburg, Russia, in conjunction with the first All-Russian Conference for Rare Diseases and Rarely Used Medical Technologies. It has proved to be an efficient strategy to foster rare diseases progress in Eastern Europe. In 2011, the sixth edition⁸¹ of this initiative was held and co-organised in Istanbul, Turkey. The Bulgarian National Alliance of People with Rare Diseases initiated and organised a Balkan patient meeting on 24 March 2012 in Sofia. Leading rare diseases experts and patients from Balkan countries took part in this event. A second edition is expected in 2013.

Research activities and E-Rare partnership

National research activities

In Bulgaria, there is no specific call for rare diseases at the national fund for research, although rare disease related projects can apply. The National Plan does not envisage any official policies to stimulate research on rare diseases; it only envisages encouraging partnerships.

Participation in European research projects

Bulgaria participates in European rare disease research projects, including: RAREBESTPRACTICES, EUROGLYCANET and TREAT-NMD.

E-Rare

Bulgaria is not currently a partner of E-Rare.

IRDiRC

Bulgarian funding agencies have not yet committed national funding to the IRDiRC.

Orphan medicinal products

ICRDOD issued an updated report in September 2012 reviewing access to medicines for rare diseases in Bulgaria⁸². The report contains information on important orphan medicinal products activities and explained how they are set up in Bulgaria in 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; and conclusions.

Orphan medicinal product committee

There is currently no orphan medicinal products specialised committee in Bulgaria. Orphan medicinal products are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. In order to optimise these procedures, in 2011 the two commissions were merged into a single one under the Ministry of Health. Subsequently, the Parliament adopted in 2012 new legislation, by which a National Council for Pricing and Reimbursement of Medicinal Products would replace the Commission at the beginning of 2013. The new body would have a status of a State agency and would be responsible for both pricing and reimbursement of all medicinal products. The headquarters would be in Pleven, rather than Sofia. Medicinal products' safety will continue to be monitored by the Executive Drugs Agency.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

Orphan drugs availability in Bulgaria and patients' access to them is regulated on national level by two legal acts – Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers) and Ordinance 38 of the Minister of Health (on the list of diseases, whose outpatient treatment is covered by the National Health Insurance Fund, NHIF). Orphan drugs have a centralised market authorisation by EMA, so they are all formally registered in Bulgaria. However, to be accessible, they have to be priced and included in PDL, as well as their indicated medical condition has to be in the NHIF list of diseases according to Ordinance 38.

By the end of 2012, 24 orphan medicinal products with EMA market authorisation are priced and included in the PDL. 15 of them are reimbursed by NHIF and 9 – by the respective hospital budget. These include: Atriance, Elaprase, Evoltra, Exjade, Fabrazyme, Glivec, Litak, Lysodren, Mozobil, Nexavar, Nplate, Revatio, Revolade, Somavert, Sprycel, Tasigna, Torisel, Tracleer, Ventavis, Volibris, Votubia, Xagrid, Yondelis, Zavesca.

Despite the recent increase of these figures, institutions dealing with planning and funding for treatment and rehabilitation of patients with rare diseases still do not have actual and reliable data on the number and distribution of patients in the country and information on the compliance and effectiveness of this expensive treatment. A recent cross-sectional observational study⁸³ appearing in the journal *Health Policy* evaluated the conditions that impact orphan drug availability in Bulgaria and other Eastern European countries. The authors observe that in Bulgaria: *"All the other orphan drugs, being not reimbursed, are practically inaccessible for the individual patients because of their high price. Despite the increasing number of orphan drugs, which are being reimbursed in Bulgaria, in reality there is no significant improvement of the accessibility of treatment for rare diseases. Neither a national epidemiological registry nor expert centres for rare diseases exist. Regulation of alternative access to orphan drugs (e.g., compassionate use, off-label use) is also missing. In these conditions many patients are left without correct diagnosis, adequate treatment, follow-up and rehabilitation."* The system for determining pricing is proving detrimental to orphan drug availability. Bulgaria uses a history-based budget through which funds for orphan drug treatments are allocated annually based on the previous year's calculated needs. Thus if the population of newly diagnosed patients grows, medicinal treatment shortages and access limitations also increase. The inclusion of new drugs in the country's reimbursement scheme results from improved awareness for rare diseases among physicians and patient associations, as well as the intentions of pharmaceutical manufacturers to market their products in Bulgaria. The authors outline the flaws with the current EU pricing system: *"In Bulgaria, the mechanism of smallest value from a set of international reference prices reduces the opportunities for flexible solutions. The inclusion of reference countries with floating euro exchange rate makes the pricing of orphan drugs dependent on the macroeconomic indicators in these countries and thereby allowing serious fluctuations of the price. This is a*

⁸² Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2012_EN.pdf

⁸³ <http://www.ncbi.nlm.nih.gov/pubmed/22939047>

specific reason for the reluctance of some companies to register prices of their orphan drugs in the small Eastern European non-Eurozone countries. Financial difficulties in one country may lead to lower prices in all referring ones. It should be also underlined that Member State authorities have little negotiating leverage since these medicines have no therapeutic alternative". Another important element that negatively impacts small countries is a lack of clinical data around the cost-effectiveness of rare disease medicinal products. Epidemiological rare disease registries are needed to improve knowledge in this area. Thus the authors call for a reformed orphan drug policy-making process that is transparent, and based on a convergence of medical, economic, ethical and social elements.

Orphan medicinal product pricing policy

There is no specific orphan medicinal product pricing policy and orphan medicinal products are subject to the general conditions as any other medicaments. The negotiation of price and level of reimbursement of orphan medicinal products in Bulgaria is determined by the Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers), and it is based on reference pricing, using data from Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal, Italy, Finland, Denmark, Slovenia, Spain, Belgium, Czech Republic, Poland, Latvia and Hungary.

Orphan medicinal product reimbursement policy

There is no specific orphan medicinal product reimbursement policy and orphan medicinal products are subject to the general conditions as any other medicaments. Medicinal products' reimbursement is regulated on national level by two legal acts – Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers) and Ordinance 38 of the Minister of Health (on the list of diseases, whose outpatient treatment is covered by the National Health Insurance Fund, NHIF). To be accessible, orphan drugs have to be priced and included in PDL, as well as their indicated medical condition has to be in the NHIF list of diseases according to Ordinance 38.

Other initiatives to improve access to orphan medicinal products

No information reported.

Other therapies for rare diseases

No information reported.

Orphan devices

No information reported.

Specialised social services

Respite care services and therapeutic recreational programmes are provided in certain medical centres in Bulgaria and are partially reimbursed by the National Health Insurance Fund.

In Bulgaria, there are currently no specialised programmes for people for rare diseases: these patients are forced to seek alternatives in the existing general schemes for the rehabilitation and integration of people with disabilities which do not often meet European standards and recommendations in the area. They are unevenly distributed across the country and public awareness of these services is low. In addition, rare disease patients may be denied access as the Territorial Expert Medical Commission's legislation is not adapted to the specificities of rare disease. As such, one of the priorities of the National Plan is to work on an integrative approach and specialised programmes for physical and social rehabilitation of rare disease patients, however no progress has been made to date, and patients feel that specialised services for rare diseases should not be separated or be in opposition to current programmes for people with disabilities.

1.4. CYPRUS

Definition of a rare disease

Stakeholders in Cyprus accept the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

The Cyprus National Strategic Plan for Rare Diseases⁸⁴ (CNSPRD) was established following the European Council's Recommendation that each Member State should develop a national plan or strategy on rare diseases, preferably by the end of 2013. The final version of the CNSPRD was developed by a national steering committee for rare diseases, which consisted of Ministry of Health officials, experts in various fields relating to rare diseases as well as patient representatives, following a public consultation (the second) with local stakeholders including patient's representatives, in March 2012. The CNSPRD was approved by the Council of Ministers of the Republic of Cyprus in November 2012.

The main objective of the National Strategic plan is to ensure that patients with rare diseases will have access to high quality care (diagnostics, treatments as well as rehabilitation for those living with the disease). The CNSPRD is based on the following 5 pillars:

- (a) Prevention – Early Diagnosis
- (b) Treatment and Management
- (c) Palliative Care / Social Inclusion / Support
- (d) Registries/Epidemiology
- (e) Research

Following the approval of the CNSPRD, the National Committee for Rare Diseases was appointed by the Council of Ministers with the task of implementing as well as monitoring the progress of the plan. In addition, the National Committee for Rare Diseases is responsible for defining a number of priority actions with objectives and follow-up mechanisms.

Centres of expertise

Currently, no officially designated centres of expertise for rare diseases exist in Cyprus since official guidelines and procedures are yet to be established at the administrative level. Nevertheless, a number of institutions are currently functioning at the level of centres of expertise. Among these are the Cyprus Institute of Neurology and Genetics, the Makarios Hospital for Mother and Child and its specialised clinics, the Cyprus Thalassaemia Centre, the Centre for the Study of Hematological Malignancies, the Bank of Cyprus Oncology Centre as well as a number of specialised clinics and departments at the Nicosia General Hospital and other hospitals. The Cyprus Institute of Neurology and Genetics operates as a centre of research, treatment and management for various rare neurological and genetic conditions. The Clinical Genetics Clinic, located both at the Cyprus Institute of Neurology and Genetics and the Archbishop Makarios III Hospital, is involved in the management of over 3500 patients and their families living with or at risk of a genetic condition in Cyprus. The Archbishop Makarios III Hospital for Mother and Child, in Nicosia, is the main referral hospital for children and adolescents where most young patients with rare diseases are referred for diagnosis and management. Several specialised clinics in this hospital operate as referral clinics for rare diseases by specialty such as, paediatric endocrinology/ nephrology/ cardiology/ neurology/ pulmonology/ infectious diseases, etc. The Cyprus Thalassaemia Centre is the main centre for screening (premarital), counselling and management of thalassaemia on the island. The Centre is based in Nicosia but also holds special clinics for the management and care of patients with hemoglobinopathies in all other public hospitals on the island. The newly established Centre for the Study of Hematological Malignancies operates as a centre of research and diagnosis of various rare haematological malignancies while management is offered by the Haematology clinics of the Nicosia and Limassol General Hospitals. The Bank of Cyprus Oncology Centre and the Oncology department of the Nicosia General Hospital are the main referral centres for the diagnosis, management and treatment of rare cancer syndromes. Several other departments and specialised clinics serve as referral centres for rare disorders including but not limited to rare haematological and congenital heart disorders, cardiomyopathies, etc. The majority of these clinics are based at the Nicosia General Hospital.

The procedure for officially designating Centres of Expertise for rare diseases in Cyprus is currently under discussion.

Registries

There is currently no designation process for rare disease registries in Cyprus, but this will be one of the considerations of the National Plan for Rare Diseases. Several registries have been formed by physicians and

⁸⁴ [http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/\\$file/Strategic%20Plan%20Rare%20Diseases.pdf](http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/$file/Strategic%20Plan%20Rare%20Diseases.pdf)

scientists at various specialised clinics and laboratories. Also a few patient organisations have their own registries based on their members. Cyprus participates in the EURO CARE CF European registry.

Neonatal screening policy

There are nationwide schemes for neonatal screening, which include screening for phenylketonuria and congenital hypothyroidism. Also a nationwide screening for congenital hearing deficit exists. An advisory committee has been established by the Minister of Health with the task of addressing the current situation of newborn screening in Cyprus and to evaluate the new emerging needs and possible expansion of the offered screening program. The committee has drafted a report summarizing their findings and highlighting Cyprus's future needs. The report is currently under review by the Ministry of Health officials.

Genetic testing

Genetic testing is available for many genetic disorders. This includes conventional and molecular cytogenetics, screening for metabolic disorders, neurogenetics, genetic testing for inherited cancers as well as for other predisposition genes, thalassemia molecular diagnostics, screening for other haematological genetic disorders and many others. In summary, diagnostic tests are available in Cyprus for around 220 genes and an estimated of 110 rare diseases⁸⁵.

National alliances of patient organisations and patient representation

In June 2010, the Cyprus Alliance for Rare Disorders (CARD)⁸⁶ was established with the aim of uniting the voices of all patients with rare diseases at a national level. The principal goals of the Alliance are the following: to lend support to the national rare disorders programme; to support the efforts of rare disease patients for improvement of prevention, medical treatment, as well as social and other services related to each of the rare disorders to improve the health and quality of life rare diseases patients; to provide support and continuous education to the patients and their families concerning the latest developments in medicine and research; and to raise awareness regarding rare diseases in the Cypriot society. Now legally registered, the Cyprus Rare Disease Alliance is becoming Cyprus' representative for patients in health organisations and institutions at European and international level. Furthermore many other patient organisations exist, representing (but not exclusively) rare disease patients with a disability such as vision deficit or hearing loss, patients with mental retardation, patients with Down syndrome, patients with congenital heart disorders, etc.

Sources of information on rare diseases and national help lines

Orphanet activities in Cyprus

Since 2004 there is a dedicated Orphanet team in Cyprus, currently hosted by the Archbishop Makarios III Medical Centre Clinical Genetics Department. This team was designated in 2010 as the Orphanet National team for Cyprus by the Medical and Public Health Services of Cyprus. The Orphanet Cyprus team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Cyprus for entry into the Orphanet database. A national website of Orphanet Cyprus⁸⁷ is also operational aiming to provide information on local activities in the field of rare diseases.

Official information centre for rare diseases

There is no official information centre for rare diseases in Cyprus apart from Orphanet.

Help line

Currently, no rare disease help line is operational in Cyprus.

Other sources of information

The Cyprus Institute of Neurology and Genetics is the main source of information for several neurological and other genetic disorders. Information on rare diseases is also published by Gene Net Cyprus⁸⁸, a project that aimed to create a bicomunal network for genetic diseases bringing together health professionals patients and families. The project has produced trilingual leaflets on genetic conditions in Cyprus: 6 leaflets were published in English, Turkish and Greek. All these documents are available on the Gene Net website which provides links

⁸⁵ Source : Cyprus Institute of Neurology and Genetics

⁸⁶ http://www.thalassaemia.org.cy/cyprus_alliance.html

⁸⁷ <http://www.orpha.net/national/CY-EL/index/homepage/>

⁸⁸ <http://www.genenet.org.cy/English/index.htm>

to Orphanet. Furthermore, the Thalassemia National Centre is the main source of information for haemoglobinopathies. In addition, several specialised clinics and organisations, which operate in Cyprus are functioning as sources of information for specific disorders.

Best practice clinical guidelines

Internationally accepted best clinical practice guidelines are being used in Cyprus as reference documents.

Training and education initiatives

Activities have been organised in this field with a training/education angle, including conferences, courses and lectures within main and teaching hospitals, especially the paediatric department of the Makarios Hospital and the Cyprus Institute of Neurology and Genetics, and also within meetings of local scientific societies. These included teaching lectures and presentations on rare genetic syndromes and rare metabolic disorders. The Cyprus Institute of Neurology and Genetics serves also as a satellite centre to the EGF courses which include several activities on rare genetic disorders.

National rare disease events in 2012

The Ministry of Health organised a seminar on 1 March 2012 to honour Rare Disease Day. The seminar was addressed by the Minister of Health and was attended by many health professionals, scientists and stakeholders in the field of rare diseases as well as patients and their representatives. During the seminar, members of the National Steering Committee, presented the first draft of the National Strategic Plan for Rare Diseases, followed by discussion and public consultation. Other rare disease-related events in 2012 included the Inherited Neurological Disorders Seminar organised by the Cyprus Society of Human Genetics and the Neurological Society of Cyprus (2 February 2012, Nicosia), the Familial Cancer Management Seminar organised by the Cyprus Oncological Society and the Department of EM / Molecular Pathology of the Cyprus Institute of Neurology and Genetics (22 March 2012), the Galactosemia seminar organised by the Pediatric Clinic of the Makarios III Hospital and the Biochemical Genetics Department of the Cyprus Institute of Neurology and Genetics (29 March 2012), the 8th Postgraduate Pediatrics Conference (which included topics on rare metabolic diseases and rare genetic diseases) organised by the Pediatric Clinic of the Makarios III Hospital in April 2012. Additionally, several events took place combining scientific seminars and public awareness such as the Scleroderma International Day.

Hosted rare disease events in 2012

Cyprus hosted a number of rare disease related events including: the 3rd Pan-European Conference on Haemoglobinopathies and Rare Anaemias organised by the Thalassaemia International Federation in October 2012, the XIIth NeuroMediterranée Conference, organised by the Cyprus Institute of Neurology and Genetics, the Cyprus Neurological Society and the NeuroMediterranée Society in November 2012, the 3rd International Conference of the Cyprus Society of Human Genetics in November 2012, and the 3rd Thalassemia Conference organised by the Cyprus Institute of Neurology and Genetics and the Cyprus Thalassaemia Centre in November 2012. Furthermore, experts in the management and treatment of various rare diseases presented the latest advancements in their fields of expertise as part of general or more specialised medical conferences.

Research activities and E-Rare partnership

National research activities

There are no dedicated research funds for rare diseases in Cyprus. In general funding opportunities are offered by the Cyprus Research Promotion Foundation and the Cyprus Institute of Neurology and Genetics. In addition, Telethon is organised by the Cyprus Institute of Neurology and Genetics (CING) to support scientific research, including research on rare diseases.

Participation in European research projects

Cyprus participates, or has participated, in European rare disease research projects including: EUROPEAN LEUKEMIA NET, Ithamet, LEISHMED and MYELINET.

E-Rare

Cyprus is currently not a member of E-Rare and does not participate in their calls.

IRDIRC

Cyprus is not currently a committed member of the IRDiRC.

Orphan drugs

Orphan drug committee

No specific activity reported.

Orphan drug incentives

No specific activity reported.

Orphan drug market availability situation

No specific information was reported on the orphan drugs marketed in Cyprus. Several orphan drugs have been requested through the Department of Pharmaceutical Services of the Ministry of Health and they were approved for use, i.e. Enzyme Replacement Treatment namely for Gaucher, Maroteaux–Lamy and Pompe disease patients. Other orphan drugs were also requested.

Orphan drug pricing policy

No specific activity reported.

Orphan drug reimbursement policy

No specific activity reported.

Other initiatives to improve access to orphan drugs

Reimbursement is available for the compassionate use of orphan drugs.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

Social services for patients suffering of disabilities as a result of rare disorders are in place. The legislation is not specific to rare diseases but concerns the nature of the disability.

1.5. CZECH REPUBLIC

Definition of a rare disease

Stakeholders in the Czech Republic accept the definition outlined in the European Regulation on Orphan Medicinal Products of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

In October 2010, the Czech Republic released for the first time a ten-year strategy (2010-2020) for rare diseases. The strategy was approved by the government on 14 June 2010. The Czech strategy intends to “ensure the effective diagnosis and treatment of rare diseases, ensure that all patients with rare diseases have access to the indicated, high-quality health care, and ensure their subsequent social integration on the basis of equal treatment and solidarity”, and is “fully compliant with the European Council’s recommendation mainly concerning improved identification of rare diseases, support for the development of health policy and the development of European-level cooperation, coordination and regulation in this field”. The Strategy outlines existing efforts and proposes major targets and measures for improving the situation in the Czech Republic, which are to be subsequently specified in more detail in the context of a three-year National Action Plan that will establish “sub-tasks, instruments, responsibilities, dates and indicators for fulfilling individual tasks”.

The first meeting of the working party for the preparation of the National Action Plan convened on 12 November 2010 in Prague and since then a dedicated taskforce (“*Meziresortní a mezioborová komise pro vzácná onemocnění* – Interministerial and interdisciplinary commission for rare diseases”, henceforward

“Taskforce”), under scientific coordination of Prof. Milan Macek (Czech National Orphanet Coordinator and Representative of the Czech Republic on the EUCERD, together with his deputy Dr. Kateřina Kubáčková who serves at Czech representative in the European Medicines Agency’s Committee on Orphan Medicinal Products committee) comprised of leading rare diseases experts, biotech industry, lawyers, the State Institute for Drug Control, medical statisticians and health insurance representatives, has convened every other month. This Taskforce created dedicated working parties with the aim to establish the basis for the National Action Plan by 2013. The Czech ten-year strategy⁸⁹ reveals the budgetary sources for the plan, which will include “existing budgetary chapters and domestic and foreign subsidies” such as the Ministry of Health⁹⁰, Ministry of Labour and Social Affairs⁹¹ and the country’s public health insurance companies (e.g. the General Health Insurance Company⁹²). A budget for the strategy has not yet been announced and is in the process of substantiation by the Taskforce. The Ministry of Health has been trying to assure funding within the framework of the EEA Norway Grants scheme (2008-2014) for the National Coordination Centre at University Hospital Motol⁹³ and via annual Ministry of Health targeted appropriation schemes, both which had been awarded in September 2012.

A group of stakeholders gathered in 2011 (including the Ministry of Labour and Social Affairs, experts and payers) to elaborate the Czech National Plan for Rare Diseases for 2012-2014⁹⁴, which on 29 August 2012, the Czech government adopted via Decree 633. The plan delineates concrete actions identified in the 2010-2020 Czech National Strategy⁹⁵. Specific areas include: Improving information; Education; Prevention; Improving screening and diagnosis; Improving the availability and quality of care; Improving quality of life and social inclusion; Support for rare disease science and research; Unification and development of data collection and rare disease biological samples; Supporting and strengthening patient organisations; Interdepartmental and interdisciplinary collaboration; and International cooperation. Besides diagnostics and treatment, the Czech National Plan encompasses research, public information, training for health professionals (both paediatric and adult specialists), and quality of life for patients in collaboration with the Ministry of Social Affairs. The Ministry of Health has opened targeted appropriation funding calls for the implementation of the Czech National Plan in December 2012.

Care for rare diseases is planned to be concentrated in 10 to 20 expert centres. The 2011 EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States were officially adopted by the Interministerial and interdisciplinary commission for rare diseases as a basis for the *de iure* establishment of rare disease expert centres in the country. The Ministry of Health plans to issue a series of public tenders for the establishment of rare diseases expert centres based on these criteria for selected groups of diseases. The aforementioned EUCERD guidelines are intended to serve as basis for the crossborder health care in rare diseases related to the implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients’ rights in cross-border healthcare⁹⁶

Centres of expertise

Based on the work of the Interministerial and interdisciplinary commission for rare diseases in 2011 and early 2012, including the entry into force of Law 372/2011Sb which in its article 112 provided legal basis for establishment of expert centres (not only for rare diseases), a group of rare disease centres was officially established on 28 May 2012 and published in Bulletin n. 4 / 2012 of the Czech Ministry of Health⁹⁷ – section 4 “Basic network of rare disease centres”. These centres include a) the National Coordination Centre for rare diseases in the Prague-Motol Teaching Hospital of Charles University Prague⁹⁸ in collaboration with the University Hospital of Masaryk University Brno⁹⁹ for the sake of regional representation, b) five regional centres of cystic fibrosis (Prague – Motol Teaching Hospital of Charles University Prague¹⁰⁰, Brno Teaching Hospital of Masaryk University¹⁰¹, Olomouc Teaching Hospital¹⁰² of Palacky University, Hradec Králové Teaching Hospital of

⁸⁹ http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf

⁹⁰ www.mzcr.cz

⁹¹ www.mpsv.cz

⁹² www.vzp.cz

⁹³ http://www.mfcr.cz/cps/rde/xchg/mfcr/xsl/Financial_Mechanism_EEA.html

⁹⁴ http://www.eucerd.eu/?post_type=document&p=2105

⁹⁵ http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf

⁹⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>

⁹⁷ http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012_6288_2510_11.html

⁹⁸ www.ublg.lf2.cuni.cz

⁹⁹ www.fnbrno.cz

¹⁰⁰ www.fnmotol.cz

¹⁰¹ www.fnbrno.cz

¹⁰² www.fnol.cz

Charles University Prague¹⁰³ and Pilsen Teaching Hospital of Charles University Prague¹⁰⁴) covering all regions of the country (children and adults with the disease), linked via a dedicated disease-specific registry¹⁰⁵, c) national centre for epidermolysis bullosa at the Faculty Hospital Brno of the Masaryk University associated with DebraCZ¹⁰⁶ and the d) Centre for inherited metabolic disorders¹⁰⁷ at the General Teaching Hospital of Charles University Prague¹⁰⁸. These centres received their status for the next three years and could be renewed following audit by the Ministry of Health. In November 2012 negotiations had started with additional centres to be created based on the EUCERD criteria. All of the planned centres operate based on their professional reputation and could be thus considered as *de facto* centres. The Interministerial and interdisciplinary commission for rare diseases aims to transform them into *de iure* centres in the future.

The value of these centres has been acknowledged by many of the country's major stakeholders including the State Institute for Drug Control, the Czech general insurance company, the Ministry of Health, patient groups, researchers and physicians. Treatment with orphan medicinal products is fully reimbursed in these centres and these centres manage the provision of very expensive orphan medicinal products.

Establishment of centres gives them government recognition, but still does not imply a dedicated budget line from health insurance companies. Treatment and diagnostics will thus continue to be provided within standard health insurance procedures administered by the General Health Insurance company (covering approximately 65% of the general population) and the "Association of Czech health insurance companies¹⁰⁹" that comprises six additional smaller health insurance companies that main have regional coverage).

However, in the future and following gradual reform of health care funding (after 2014) it is planned that respective rare diseases or related rare disease diagnostic groups will be concentrated into dedicated centres and that they will receive a dedicated budget line linked to nominal health insurance reallocation (e.g. as in The Netherlands). In this regard it is expected that the major condition for health care reimbursement would be *de iure* established centre-based care. In addition, it is expected that in duly justified instances (e.g. very rare diseases) care will be assured within European Reference Networks (i.e. in line with the EU Directive on cross-border healthcare sections 54 and 55). Currently, cross-border healthcare falls into the domain of the Centre for International Reimbursements¹¹⁰.

Registries

The Czech Republic contributes to some European registries such as ECFS.eu for cystic fibrosis¹¹¹ and TREAT-NMD for muscular dystrophies, European Porphyria Network (EPNET), EUROCAT for rare birth defects¹¹², as well as the SCNIR international registry¹¹³. The National Registry for Cancer¹¹⁴ also contains information on the distribution of rare cancers in the Czech Republic. The Interministerial and interdisciplinary commission for rare diseases is in the process of establishing the National registry of rare diseases, which will serve as a "confederated database" of all other disseminated registries in centres to be established. As a pilot projects serves the dedicated registry initiative of the Institute of Biostatistics and Analysis¹¹⁵ at the Masaryk University in Brno¹¹⁶. Finally, the National centre for cystic fibrosis in University Hospital Motol was accepted into the Clinical Trial Network¹¹⁷ of the European Cystic Fibrosis Society¹¹⁸.

Teams in the Czech Republic contribute to the following European registries: EUROCARE CF, EUROCAT, SCNIR registry and TREAT-NMD.

¹⁰³ www.fnhk.cz

¹⁰⁴ www.fnplzen.cz

¹⁰⁵ www.cfregistr.cz

¹⁰⁶ <http://www.debra.cz/>

¹⁰⁷ www.udmp.cz

¹⁰⁸ www.vfn.cz

¹⁰⁹ <http://www.szpcr.cz/>

¹¹⁰ <http://www.cmu.cz/en?Itemid=224>

¹¹¹ www.cfregistr.cz

¹¹² www.vrozene-vady.cz

¹¹³ <http://depts.washington.edu/registry/>

¹¹⁴ <http://www.linkos.cz/odbornici/onkologie/nor.php>

¹¹⁵ <http://www.iba.muni.cz/index-en.php>

¹¹⁶ www.registry.cz

¹¹⁷ <http://www.ecfs.eu/ctn>

¹¹⁸ www.ecfs.eu

Neonatal screening policy

Neonatal screening is now available for 13 disorders¹¹⁹. Neonatal screening is routinely performed for phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, hyperphenylalaninemia, maple syrup urine disease, isovaleric aciduria, glutaric aciduria type I, medium-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, carnitine palmitoyl transferase 1 deficiency, carnitine palmitoyl transferase 2 deficiency, carnitine acylcarnitine translocase deficiency and cystic fibrosis. There are follow-up clinical services available for all screened disorders and an *ad hoc* working group comprising representatives of the Czech Ministry of Health and screening institutes meets at a tri-monthly basis. Neonatal screening is fully reimbursed by the General Insurance Company¹²⁰ from 2010. In early 2011 the National Coordination Centre for Neonatal Screening was officially established by the Czech Ministry of Health¹²¹ and its operation is funded by targeted annual appropriation schemes. In 2012 the ongoing research grant from the Czech Ministry of Health has enabled a pilot project for broadening of the scope of screened metabolic diseases by mass spectrometry. Its outcomes will be published in 2013. The information portal for lay public and physicians on neonatal screening was established and financed by the Czech Ministry of Health¹²².

Genetic testing

Genetic tests are registered for 223 genes and 285 diseases in the Orphanet database¹²³. Genetic counselling exists for all families at risk and 45 such facilities are currently registered¹²⁴, which mostly collaborate with molecular genetic and cytogenetic laboratories. Clinical genetics services are available throughout the entire country, with every major district having such services, both at private and/or state based levels. Genetic services are carried out in compliance with all international professional standards and are fully covered by the national health insurance system.

In November 2011 a new law On Specific Health Care Services 373/2011 Sb was passed. Act 373/2011 Sb regulates genetic testing for rare diseases and reflects the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (CETS No 203) which regulates Direct to Consumer (DTC) testing via specific informed consent provisions. It stipulates (Part 6; section 28) that germinal genome is allowed to be tested within the context of rare diseases in genetic laboratories that are accredited according to the ISO 15189 norm, in accordance with "OECD guidelines for quality assurance in molecular genetic testing"¹²⁵. Moreover, new law 372/2011 Sb stipulates provisions regarding informed consent procedures in the domain of health care services. This law came into effect in the Czech Republic on 1 April 2012.

National alliances of patient organisations and patient representation

In December 2011 the foundations were established for the creation of an overarching Czech National Alliance for Rare Diseases¹²⁶, which was officially established in February 2012 (received official registration from the Czech Ministry of Interior) and became member of Eurordis in May 2012. As of December 2012 this alliance linked together 24 individual patient support groups via a democratic, bottom-up, activity spearheaded by several larger patient support groups. Its members meet approximately every 3 months, publish a newsletter, run awareness campaign in the media, co-organised one Czech Parliament hearing on rare diseases. The Czech National Alliance also works in association with the Coalition for Health Association¹²⁷, which also has common disease representatives. Both alliances will collaborate on topics of common interest, mainly in the social services domain. The Ministry of Health had issued appropriation schemes for the operation of these alliances in October 2012. In June 2012 representatives of the Czech National Alliance joined the Interministerial and interdisciplinary commission for rare diseases.

¹¹⁹ <http://www.novorozenecky-screening.cz/>

¹²⁰ www.vzp.cz

¹²¹ www.novorozenecky-screening.cz

¹²² <http://www.novorozeneckyscreening.cz/>

¹²³ Data extracted from Orphanet in December 2012.

¹²⁴ <http://www.slg.cz/pracoviste/klinicka-genetika/>

¹²⁵ <http://www.oecd.org/dataoecd/43/6/38839788.pdf>

¹²⁶ www.vzacna-onemocneni.cz/

¹²⁷ www.koaliceprozdravi.cz

Sources of information on rare diseases and national help lines

Orphanet activities in the Czech Republic

Since 2006 there is a dedicated Orphanet team in the Czech Republic, currently hosted by the University Hospital Motol and the Second Faculty of Medicine of Charles University Prague, that has been transformed by the Bulletin n4/2012 into the National Coordination Centre for Rare Diseases (see above). The team was designated as the Czech national Orphanet team by the Ministry of Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also maintains the Orphanet Czech Republic national website¹²⁸ in the Czech language providing an entry point to the database. The informatics group of the National Coordination Centre for Rare Diseases also runs the dedicated website financed by the Ministry of Health for the general population and physicians on rare diseases¹²⁹.

Official information centre for rare diseases

There is no official information centre for rare diseases in the Czech Republic other than Orphanet and the first steps for the establishment of such a centre were started in Autumn within the framework of the National Coordination Centre for Rare Diseases at University Hospital Motol¹³⁰.

Help line

A help line for rare diseases is under preparation and is planned to be funded within the Norway Grants mechanism with the National Coordination Centre for Rare Diseases in University Hospital Motol and by dedicated appropriations from the Czech Ministry of Health in 2013.

Other sources of information

Patient organisation web sites are one of the few national sources of information for rare diseases in the Czech language¹³¹. The National Alliance for Rare Diseases¹³² has started to prepare an integrated server which will unify all disseminated resources under one web portal, including current and expanded neonatal screening¹³³.

Good practice guidelines

Best practice guidelines for genetic diagnosis are listed at the website of the Czech Medical Genetics Society of Czech Medical Association of Jan Evangelista Purkyně for the more common rare diseases¹³⁴ and reflect e.g. the EMQN.org and Eurogentest.org guidelines.

Training and education initiatives

Rare disease information was added into the medical genetics training curriculum at the Masaryk University Brno¹³⁵ (4th year) and Charles University Prague – 2 Faculty of Medicine (5th year¹³⁶).

National rare disease events in 2012

A number of events were organised by rare disease patient organisations in the Czech Republic to mark Rare Disease Day 2012, including the first major meeting on 24 February 2012 of patient organisations and patient representatives with the goal of establishing a Czech Association for Rare Diseases to connect all patients and patient organisations with the aim of raising awareness about rare diseases and their impact on patients' lives amongst the general public and decision-makers. In addition, the Czech National TV station CT1 broadcasted a documentary about rare diseases on 15 February 2012. In September 2012 the second cycle of interviews on rare diseases was initiated at Radio ClassicFM Prague.

Hosted rare disease events in 2012

Amongst the events announced in OrphaNews was: the 6th International Symposium on Childhood MDS and Bone Marrow Failure syndromes (7-9 November 2012, Prague).

¹²⁸ <http://www.orphanet.cz/national/CZ-CS/index/%C3%BAvod/>

¹²⁹ www.vzacnenemoci.cz

¹³⁰ www.vzacnenemoci.cz

¹³¹ <http://vzacna-onemocneni.cz/odkazy/>

¹³² www.vzacna-onemocneni.cz

¹³³ <http://novorozenecky-screening.cz>

¹³⁴ <http://www.slg.cz/koordinacni-centrum-geneticky-laboratori>

¹³⁵ www.muni.cz

¹³⁶ www.lf2.cuni.cz

Research activities and E-Rare partnership

National research activities

Rare diseases research is conducted under several funding bodies: the internal grant agency of the Czech Ministry of Health (www.mzcr.cz), the grant agency of the Czech Republic (www.gacr.cz), and the grant agency of the Charles University Prague (www.gauk.cz). Currently around 15 different research projects in the field of rare diseases are registered with Orphanet, focusing on around 30 different rare disorders. At least three projects are targeting specific genes. The Czech Republic also participates in many international-level activities including ERNDIM (a consortium for quality assessment in biochemical genetics for rare disease).

Participation in European research projects

Teams in the Czech Republic participate, or have participated, in the European rare disease research projects, including: CLINIGENE, ENCE PLAN, EUMITOCOMBAT, EURO-PADNET, EURO CARE-CF, EUROPEAN LEUKEMIA NET, EURO GENTEST, EURO GLYCANET, HUE-MAN, MYORES, NEUROSI, INTREALL, OPTATIO, MABSOT, PNSEURONET, RD PLATFORM, RDConnect, SARS/FLU VACCINE, SCRIN-SILICO and SIOPEN-R-NET.

E-Rare

The Czech Republic is not currently a partner of the E-Rare research programme on rare diseases.

IRDiRC

Czech funding agencies have not yet committed funding to the IRDiRC.

Orphan medicinal products

SUKL¹³⁷, the State Institute for Drug Control, is the regulatory body in the Czech Republic responsible for the regulation and surveillance of human medicinal products and medical devices, including orphan medicinal products.

Orphan medicinal product committee

There is no permanent committee for orphan medicinal products in the Czech Republic.

Orphan medicinal product incentives¹³⁸

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, the Czech Republic has a number of mechanisms in place to encourage orphan medicinal product development. For example *"administrative fees are not charged for applications for the registration of medicinal products or for an amendment, extension or transfer of registration of a medicinal product or for authorisations for parallel import of a medicinal product, if the application concerns a medicinal product included in the register of orphan medicinal products under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.*

"Under §65(2)(b) of Act No 79/1997 Coll. on medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may refrain from recovering costs where these concern operations which are in the public interest or may have especially important implications for the wider population. These operations include applications for: authorisation/registration of clinical assessments of medicinal products and notification to the submitter of additions to the records in cases concerning the evaluation of an orphan medicinal product, and consultation and opinions on such applications; application for registration of an orphan medicinal product and application for amendment, extension or transfer of registration or application for authorisations for parallel import of an orphan medicinal product and consultation and opinions on applications concerning orphan medicinal products.

"Under §26d(1) of Act No 79/1997 Coll. On medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may, in the case of orphan medicinal products in justified cases meeting the conditions laid down by decree, allow the registration of a medicinal product or the placing on the market of individual batches of a medicinal product even where the data are indicated on the packaging in a language other than Czech."¹³⁹

¹³⁷ www.sukl.cz

¹³⁸ This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp9-10)

¹³⁹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp9-10)

Orphan medicinal product pricing policy

There is no specific pricing mechanism for orphan products. The prices of pharmaceuticals in Czech Republic are based on reference ex-factory prices in European Union countries. The maximum ex-factory price is calculated as mean of three lowest EU reference prices. The ex-factory price is then increased by wholesaler and pharmacy margin and value added tax.

Orphan medicinal product market availability situation

In 2012, 62 orphan medicinal products were registered in the Czech Republic, of which 45 have been launched on the market (Afinitor, Aldurazyme, Arzerra, Busilvex, Cystadane, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedea, Peyona, Prialt, Replagal, Revlimid, Revolade, Somavert, Tassigna, Tepadina, Torisel, Tracler, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Yondelis, Zavesca).

Orphan medicinal product reimbursement policy

Not all orphan medicinal products are reimbursed; the 45 which are distributed on a centre basis are fully reimbursed (Afinitor, Aldurazyme, Arzerra, Busilvex, Cystadane, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedea, Peyona, Prialt, Replagal, Revlimid, Revolade, Somavert, Tassigna, Tepadina, Torisel, Tracler, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Yondelis, Zavesca). In some cases the level of reimbursement is according to individual negotiation between expert centres and marketing holders. Establishment of official expert centres via Bulletin 4/2012 (see above) will facilitate subsequent reimbursement negotiations with health insurance or pharmaceutical companies (e.g. clinical trials, compassionate use programmes, risk sharing strategies etc.). Alternatively, there is the possibility to use art. 16 of Law 48/1997 Sb for the "Individual patient reimbursement scheme". This scheme is applicable only in the case of unavailability of alternative treatments. Specialised centres can apply within a revolving application scheme to a commission comprising major stakeholders (e.g. the Czech Ministry of Health, State Institute of Drug Control and Health insurance companies) until the official reimbursement procedure is instituted for the given orphan medicinal product. This measure is mainly intended to "bridge" the period between e.g. phase 3 clinical trials and introduction of a successful drug into health insurance reimbursement schemes.

Currently there is no special reimbursement procedure for orphan medicinal products and there are assessed similarly to non-orphan medicines. Since 2008 there is in place mandatory pharmacoeconomic assessment rules requiring cost per additional QALY calculation. The reimbursement of drugs is assessed by State Institute for Drug Control (SUKL) and the process is open only to pharmaceutical companies and health insurance funds. Patient groups and healthcare professional are not involved. Since the beginning of 2013 the new willingness to pay threshold has been introduced reflecting 3-times GDP per capita (est. 1,1 mil. CZK/QALY). The orphan drugs are not able to provide the cost/QALY results below this threshold either they do not have sufficient and long-term clinical data or their ICERs are exceeding the threshold. So called "highly innovative drugs" not presenting cost-effectiveness calculations may get conditional reimbursement for maximum 3 year. The real-clinical data must be collected and analyzed. At the end of the provisional period the cost-effectiveness (cost per QALY) is re-evaluated and willingness-to-pay threshold is strictly applied. As the majority of orphan drugs are not able fulfil the 3GDP per capita rule they will be excluded from the reimbursement after 3 years.

Other initiatives to improve access to orphan medicinal products

The country has compassionate use programme for specific orphan medicinal products, and therapeutic programmes that allow for the use of certain non-authorised medicinal products, usually coordinated by specific centres, on a named-patient basis. *Ad hoc* committees exist for very expensive orphan medicinal products, which are centre-based.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

A few patient organisations also offer recreational services, such as summer camps for children or rehabilitation/therapeutic weekends for adult patients. These are usually fully reimbursed by the Ministry of Social Affairs. The *Act on social services for people with disabilities* came into force in 2007, improving the access to social services for rare disease patients: these schemes are reimbursed and are fully funded from social insurance and are coordinated by the Ministry of Social Affairs.

1.6. DENMARK

Definition of a rare disease

There is no official absolute definition for rare diseases at the moment in Denmark. The Danish Health and Medicines Authority (formerly National Board of Health) tends to define rare diseases as affecting no more than 500 - 1000 patients in the Danish population. Rare Disorders Denmark (The national alliance of patient organisations for rare disorders) defines rare diseases as affecting no more than 1 000 patients in the Danish population. The Danish definition also takes into account the degree of complexity of the disease, and the general rules that the disease must be severe, genetic or congenital, therefore rare cancers and infectious diseases are usually not considered to be part of the concept of “rare diseases” in Denmark, but it is recognised that they have similar problems.

National plan/strategy for rare diseases and related actions

Access to health care at hospitals and GPs is free of charge for all citizens independently of diagnoses and prevalence. Patients also have a right to choose between relevant hospitals. Access to social services and support for patients is also free of charge and given depending on need.

There is currently no specific national/strategy plan for rare diseases in Denmark involving all sectors, but regarding the hospital sector the Danish Health and Medicines Authority as the statutory competent authority has approved centres of expertise/referral centres for rare diseases in 2010 as part of a comprehensive planning of highly specialized hospital services in Denmark accordingly to the health care act.

Since 1993 The National Board of Health has published a list of centres of expertise designated by the National Board of Health. This list of centres has been revised regularly through the years and is now developed to the above mentioned approval system.

In 2001 the Danish National Board of Health launched a special report on rare diseases with recommendations regarding rare diseases in general and specific recommendations for 14 rare diseases to be cared for at two specialised Rare Diseases Centres. These two centres were established in Copenhagen and Aarhus respectively. In the beginning the centres were mainly focused on paediatric patients. Now about one third of the patients are adults. The two centres work continuously on strengthening the interdisciplinary and cross professional activities. The 2001 report also gave a number of other recommendations which have not yet all been implemented. The report described an ideal general model for development of activities regarding rare diseases in the health care sector and cooperation with other sectors. Many of the EUROPLAN-recommended elements of a national strategy for rare diseases are dealt with in this report.

Current expenditure for rare diseases, as for all other diseases, is within in the general health system budget of the regions and municipalities. There are no dedicated funds for rare diseases, except for the dietary treatment of phenylketonuria which is directly financed from the state budget. In 2010 special funding was obtained from the state budget to implement a National Center for Rett syndrome within the Kennedy Center.

On 19 November 2010, Rare Disorders Denmark in collaboration with EURORDIS held a National Conference on Rare Diseases¹⁴⁰ in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark. In 2011 it was decided to let the National Board of Health establish a working group to elaborate a national strategy for Rare Diseases.

The working group with the task to elaborate a national plan for RD has a broad representation of stakeholders and was founded at the end of 2011 and met at the start of February 2012 for the first time. The

¹⁴⁰http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_denmark_europlan.pdf

recommendations in the previous report on rare diseases from 2001 are being assessed to see what is still needed, what has changed and what new recommendations can be added considering the European perspective and the recommendations for a national strategy. The subject of centres of expertise is a key area of consideration. The working groups' proposal for a national strategy/ plan is scheduled to be ready in Autumn 2013.

Centres of expertise

The Danish Health and Medicines Authority has the authority to approve centres of expertise accordingly to the Health Care Act.

As mentioned above two centres of expertise specific for rare diseases have been functioning officially since 2001 in the health care system in Denmark at university hospital level. There are also a number of other established referral centres/centres of expertise approved by the Danish Health and Medicines Authority with the task to maintain a specific or several specific rare diseases¹⁴¹.

The two centres, Clinic for Rare Disabilities – KSH in Copenhagen and Centre for Rare Diseases – CSS in Aarhus, were established in 2001, being responsible centres for 14 specific diagnoses. The special remit of these centres is the co-ordination of patient-care programs, treatment protocols and databases, and taking care of medical highly specialised tasks in agreed partnerships. Two years after the establishment of the centres, Rare Diseases Denmark conducted a survey that revealed that 75% of patients felt they had received better and more coherent treatment when treated at the centres. The two centres also have an important function in assessing patients, who do not have a diagnosis, but where a rare disease is suspected. Today the centres take care of many more different diagnoses, which do not have another nominated centre of expertise.

According to the Danish Health Care Act from 2007 the National Board of Health began a comprehensive work going through the organization of specialized diagnoses, treatments and medical technologies across 36 surgical, medical and diagnostic specialties. The main goal was to improve quality through sufficient volumes of patients and experienced professionals. The general criteria for establishing centers of expertise in this context are rareness, complexity, multidisciplinary and costly technologies. In 2009 public and private hospitals could apply to the National Board of Health for approval to maintain specific specialised treatments. In 2010 the National Board of Health announced the approved hospital departments in specific lists for each medical specialty. The two Centres of Rare Diseases have also been approved in this context. The departments that host the two Centres of Rare Diseases have also been approved for a number of different rare diseases, e.g. in Copenhagen for inborn errors of metabolism (IEM).

The number of centres of expertise for a single condition or groups of conditions depends on rarity (estimated number of patients), competence and available technology. A specific condition might thus be treated at only one specialised hospital department or up to five different hospital departments. Some geographical considerations will usually play a role in the decision making process if there is room for more than one centre. The approved departments are required to secure and develop their expertise, establish a quality improvement programme, document their activities and take part in teaching and research activities. The system is focused on treatment of patients.

The National Board of Health has in the National Plan for highly specialised hospital services issued about 1100 approvals of medical highly specialised functions and estimates that about 100 of these are related to various diseases or groups of diseases which can be classified as rare. In General the approvals will last for a duration of 3 years thereafter a revision is due.

Registries

No single centralised register for rare diseases currently exists in Denmark, but a number of different registries and biobanks exist although there is currently no public register giving an overview of the existing registries and biobanks dealing with rare diseases. The Serum Institute has hosted registry and biobank of all newborn screening blood samples since 1980. The Kennedy Centre maintains biobanks on specific rare disorders as Menkes disease and various genetic eye diseases. All visually handicapped children are registered until the age of 18. Furthermore, several research departments have registries of rare diseases patients. The Raredis database which collects clinical data has been developed in Denmark in accordance to the recommendations in the Danish report of rare diseases from 2001 and has been in function since 2007 at the two Centres of Rare Diseases in Denmark. There is collected data on more than 1800 patients with 561 different diagnoses seen at

¹⁴¹ For more information

http://www.sst.dk/Planlaegning%20og%20kvalitet/Specialeplanlaegning/specialeplan_2010.aspx
Centres of Reference for RD in Europe: State of the art in 2006 and recommendations of the RDTF (p.9)
<http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

the two centres. Centres of rare diseases in the Nordic countries use their local version of Raredis for collecting clinical data. The hereby collected information can be used for research projects and bench marking at a Nordic level for different rare diseases. Specific research projects are performed and planned.

The Danish National Patient Registry (NPR) exists since 1977 and collects systematic information on diagnoses, surgical treatment, and various demographical parameters on all patients admitted to hospital or similar institutions in Denmark. The Danish personal identity numbers give possibilities to follow up patients through the years and combine data with other registries.

Denmark contributes to some European registries such as EUROCARE CF, EIMD, EMHG and EUROCAT.

Neonatal screening policy

National neonatal screening schemes are in place for phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, maple syrup urine disease, ASL, carnitine transporter defect, medium chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, very long chain acyl-coA dehydrogenase deficiency, glutaric acidemia type 1, methyl malonic acidemia, propionic acidemia, multiple carboxylase defect, arginino succinic aciduria, tyrosinemia type 1 and biotinidase defect. Furthermore, the timing for drawing the blood samples (done by heel-prick) has been brought forward from five days to within 48-72 hours following birth, allowing for earlier intervention and treatment. Neonatal hearing screening has also been introduced as part of the national policy.

Genetic testing

There are 6 approved highly specialised centres for clinical genetic testing and counselling. Some genetic testing is also carried out in a few clinical biochemistry laboratories (e.g. BRCA testing). Genetic testing abroad is possible mediated by the clinical genetics centres. Genetic testing for medical reasons is part of the national health care system and free of charge. State reimbursement of costs for tests abroad can be effected after approval from the Danish Health and Medicines Authority.

Diagnostic tests are registered as available in Denmark for 114 genes and an estimated 224 diseases in the Orphanet database¹⁴².

National alliances of patient organisations and patient representation

Rare Disorders Denmark (RDD), founded in 1985, is the national alliance of 47 rare disease patient organisations/societies covering 11,500 members. In addition there are further 20 other patient organisations for rare disorders. Patient organizations are eligible to receive limited funding from the Ministries of Health and Social Affairs. RDD facilitates exchange of experience between the member societies and advocate the rights of all rare disease patients.

Rare Disorders Denmark RDD holds a mini-roundtable with relevant pharmaceutical companies. The mini-roundtable currently has 10 members.

Rare Disorders Denmark has developed a tool, Social Profiles, to promote dialogue between rare disease patients and professionals. The profiles are currently available for 35 rare diagnoses, with more to come. The profiles are published on the "Rare Citizen" website¹⁴³.

Over 2009 -2012 Rare Disease Denmark developed a special training programme for families with children affected by rare diseases under the age of 18 called "Rare Family Days". Some preliminary results were presented by RDD at the ECRD conference in Brussels and the final results will be published in 2013, along with a new concept for "Rare Family Days".

RDD cooperates with the Centre of Disability and Social Psychiatry (ViHS). In 2012 RDD through ViHS adopted a Focus Point of Contact for very rare disease patients and relatives with no possibility to join or form a patient organisation/society. More than 500 rare citizens adhere to the Focus Point, representing more than 150 rare diseases.

Also in 2012, RDD contributed to the work of National Board of Health's working group to elaborate a national strategy for Rare Diseases. When it comes to the internal life of RDD, several activities for RDD's member organisations have been organised, including seminars, project days and more. A monthly electronic newsletter was published to more than 400 recipients. From December 2012, RDD has established its own secretariat situated in an accessible building, which holds offices for 24 disability- related organisations.

Patients' organisations are, in general, consulted regarding legalisation concerning issues relevant to rare diseases and, in general, participate in the relevant boards and official bodies/working groups. Rare

¹⁴² Information extracted from the Orphanet database (December 2012).

¹⁴³ www.sjaeldenborger.dk

Disorders Denmark is represented on an advisory board of the Centre for Disability and Social Psychiatry (ViHS) and in the working group of National Strategy for rare diseases, constituted by the National Board of Health in December 2011.

Sources of information on rare diseases and national help lines

Orphanet activities in Denmark

From 2004-2010 there was a dedicated Orphanet team in Denmark, hosted by the John F. Kennedy Institute. This team was in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in the country for entry into the Orphanet database.

Official information centre for rare diseases

The state-funded information centre on rare diseases, the Danish Centre for Rare Diseases and Disabilities (*Center for små handicapgrupper*¹⁴⁴) has been functioning since 1990 with a public database containing short descriptions in Danish on rare diseases. The centre provided information, as well as guidance, especially on social issues, and provided contact with patient organisations. The CSH also ran a rare disease help line which provided information and support. The CSH maintained a database of approximately 400 rare disease patients who are currently without patient organisation representation for their disease. The CSH also contributed to Rarelink.eu, the Nordic website compiling links relating to information on rare diseases.

At the end of 2010, the Ministry for Social Affairs closed the Centre for Rare Diseases and Disabilities (*Center for Små Handicapgrupper – CSH*) as an independent institution. This decision was a consequence of the merger of 3 information and knowledge networks and 13 research centres in areas overseen by the Ministry of Social Affairs to form a new Centre for Disability and Social Psychiatry (*Videnscenter for Handicap og Socialpsykiatri - ViHS*¹⁴⁵) as of 1 January 2011. The experience of the first years of the new structure is that the help line is less sought after than before and that the knowledge-based work with short diagnosis descriptions has become more difficult and is not at the same level as before. The future general information about rare diseases is expected to be discussed in the working group of the National Strategy.

Help line

There is established a dedicated “Rare Disability Team” within the ViHS’s counselling service which mans the help line.

Other sources of information

No specific activity reported.

Good practice guidelines

The 2001 report from the National Board of Health laid down guidelines concerning 11 specific rare diseases. These guidelines also serve as template concerning other rare diseases. Health care professionals consult published international guidelines.

Training and education initiatives

The two Rare Diseases Centres participate in educational activities for nurses and doctors. Furthermore, they provide teaching for other health care professionals, families, teachers and caretakers.

National rare disease events in 2012

Rare Disorders Denmark organised a number of events to mark Rare Disease Day 2012¹⁴⁶. A conference entitled ‘Welcome to the Land of the Rare’ focused on the provision of social support to the rare patients and their families. This conference aimed to provide input to the ongoing elaboration of the National Plan for Rare Diseases. The 150 participants at the conference included patients, their relatives, professionals and specialists in the area of social services, doctors and relevant authorities and decision makers. In addition a march to mark the day was held in Copenhagen to raise awareness of the cause. The march ended with the awarding of the Rare Disease Day prize to John Rosendahl Ostergaard received Wednesday 29 February Rare Prize for his work

¹⁴⁴ www.csh.dk

¹⁴⁵ More information on the organisation of the ViHS can be accessed here

http://www.csh.dk/fileadmin/pdf/Rapporter_og_andet/Organisering_af_ViHS-1.doc (accessed 27/01/2011)

¹⁴⁶ www.29februar.dk

for people with rare diseases and disabilities, as well as to the former chair of Rare Diseases Denmark, the late Torben Grønnebak.

Hosted rare disease events in 2012

No specific information on rare disease events hosted in Denmark were reported in *OrphaNews Europe* in 2012.

Research activities and E-Rare partnership

National research activities

There are no specific programmes for rare diseases research in Denmark or focussed calls/grants. Although there are no specific initiatives to support research into rare diseases in Denmark, Danish researchers are active in the field and there are resources in place (biobanks, registries, databases) for rare disease research.

Participation in European research projects

Danish teams participate, or have participated, in a number of European research projects for rare diseases, including: ALPHA-MAN, CILMALVAC, EURHAVAC, EIMD, EMSA-SG, EUROCRAN, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROMEDICAT, EMVDA, EUNEFRON, FNAIT, GAPVAC, HDLOMICS, HUE-MAN, HUMALMAB, IMMOMEK, INTREALL, IMPACCT, LEISHMED, MMR-RELATED CANCER, MYASTAID, NEUROKCNQPATHIES, NEUROPRION, NM4TB, PULMOTENSION, SPASTICMODELS, SIOPEN-R-NET, SERO-TB, TB TREATMENT MARKER and VACCINES4TB.

E-Rare

Denmark is not an E-Rare partner.

IRDiRC

Danish funding agencies have not committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

There is currently no committee dedicated to Orphan medicinal products and/or rare diseases in Denmark.

Orphan medicinal product incentives

Upon request, the Danish Medicines Agency may provide free scientific advice in the development of orphan medicinal products¹⁴⁷.

Orphan medicinal product market availability situation

Out of 68 orphan medicinal products with an EU market authorisation, 58 are approved in Denmark and are on the Danish national formulary of medicines¹⁴⁸. The approval process usually takes 6-8 weeks.

The list of orphan medicinal products approved and launched on the market in Denmark includes: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Ceplene, Cystadane, Diacomit, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tassigna, Tepadina, Teysuno (S-1), Thalidomide Celgene, TOBI Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, VPRIV, Vyndaqel, Wilzin, Xagrid, Yondelis, Zavesca.

Orphan medicinal product pricing policy

Manufacturers and importers of pharmaceutical products are free to set the price of each pharmaceutical. However, orphan medicinal products are mostly hospital-only pharmaceuticals, and the drugs used at hospitals are bought via public procurement. Most public tenders are carried out by AMGROS which is a hospital purchasing agency owned by the five regions in Denmark.

¹⁴⁷ This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp10-11)

¹⁴⁸ www.medicinpriser.dk

Orphan medicinal product reimbursement policy

There is no reimbursement policy that pertains specifically to orphan medicinal products. In many cases, orphan medicinal products are restricted to hospitals. All medicines dispensed at hospitals are free of charge to the patient, and if dispensed from a pharmacy on prescription there is a needs-based co-payment¹⁴⁹.

Other initiatives to improve access to orphan medicinal products

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, there are no specific programmes to facilitate the provision of medicines to rare diseases patients in Denmark (i.e. compassionate use). However, in special circumstances and to a limited degree the Danish Medicines Agency can authorise "the sale or dispensing of medicinal products that are not marketed in Denmark for other purposes than clinical investigations (cohort or named patient supply). Patients with life-threatening diseases for which there are no well-documented treatment options can be offered experimental treatment (named patient supply only)"¹⁵⁰.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

Respite care services are sometimes provided by municipalities. Patient organisations organise informal therapeutic recreational activities and can sometimes receive government financial support. Services are provided and funded by the government to enable help integrate patients with rare diseases into daily life, both at school and work.

1.7. ESTONIA

Definition of a rare disease

Stakeholders in Estonia accept the definition of the European Regulation on Orphan Medicinal Products of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

The national plan for rare diseases in Estonia is under development.

In 2008, Estonian Government adopted Eesti Rahvastiku Arengukava 2009-2020 (*Estonian National Health Plan 2009-2020*, hereafter referred to its Estonian acronym, ERTA). ERTA 2009-2020 provides recommendations and indicates the directions to be taken to improve healthcare and brings together the tasks necessary to achieve this. The plan also assembles a large number of strategic documents which have already been implemented or which are soon to be implemented in other fields that have a role to play in achieving ERTA's objective.

In September 2012 a working group was set up to discuss the activities on the field of rare diseases which will be added to the implementation plan of ERTA: the working group includes professionals in the field of rare diseases (doctors, medical geneticists, representatives of patient organisations, representatives from the Estonian Board of Disabled People, etc.). A draft plan for rare diseases was drawn up at the end of 2012. The process to finish the plan will be presented to the Minister and management team members of the Ministry of Social Affairs.

¹⁴⁹ EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl & Florian Bachner, p.47.

¹⁵⁰ This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p10)

Centres of expertise

In Summer 2011 Tallinn Children's Hospital genetics services joined with Tartu University Hospital, the United Laboratory and the Department of Genetics and thus one common Department of Genetics was formally established at Tartu University Hospital. This university provides medical training for all medical students, including practical training. Tallinn Children's Hospital genetics service became the branch office of Department of Genetics, Tartu University Hospital. All of the genetic specialty services are represented with the diagnosis and treatment of rare diseases provided for all over Estonia. As the Tartu University Hospital meets the EUCERD criteria for centres of expertise, there are no plans for a special designation procedure for centres of expertise.

Registries

Estonia does not have a national committee on registries nor national registers for groups of diagnoses and does not plan for rare disease specific registries. In Estonia all health-related information is collected to the Tervise Infosüsteem (Health Information System). Rather, overview and statistical data from about diseases, including rare diseases can be extracted from the electronic health information system using ICD-10. Estonia participates in the EUROCARE CF and EURO-WABB European registries.

Neonatal screening policy

For early detection of all developmental disorders, including rare disorders, there is a consensus agreement that all infants and children with any developmental disorders should be referred to one of tertiary children's hospitals in Estonia: Children's Clinic of Tartu University Hospital or Tallinn Children's Hospital. Both hospitals have quick access to medical genetics services for early detection and prevention¹⁵¹. Early detection or treatment of rare diseases is provided using metabolic testing, chromosomal analyses, DNA diagnostics and neonatal screening programmes are in place for phenylketonuria since 1993 and congenital hypothyroidism since 1996.

There was a request to the Health Insurance Fund to enlarge the screening policy in 2009, and it is hoped that the widened policy will come into effect in 2015. There are plans to introduce tandem mass-spectrometry analysis at Tartu University Hospital in 2013 to provide screening for 10 further diseases (fatty acid oxidation defects – MCAD, LCHAD, VLCAD, CACT, CPT I and II; amino acid disorders – tyrosinemia and maple syrup urine disease; organic acidurias – isovaleric aciduria type I and glutaric aciduria type I).

Genetic testing

Genetic testing is organised as a part of regular medical service. There is one Department of Genetics in Tartu University Hospital which performs genetic counseling and genetic testing¹⁵². This department is located in two main cities – Tartu and Tallinn and has two laboratories – molecular genetic and cytogenetic laboratories, which perform most genetic testing for everyday clinical practice. Genetic counseling is always provided before and after testing.

There are no national guidelines for genetic testing; the official guidelines¹⁵³ of European Union and European Society of Human Genetics are used.

All genetics tests which are available locally in Estonia and there are clinical indication, are reimbursed by Estonian Health Insurance Fund. Genetic testing in abroad is possible. If there are clinical indications and this test is not available locally, the assembly of doctors (minimum 3 doctors) will apply for the payment of specific genetic test abroad to the Estonian Health Insurance Fund. In case of a positive decision, the Estonian Health Insurance Fund will give out the E112 form or a guarantee letter for this specific investigation.

Diagnostic tests are registered as available in Estonia for 161 genes and an estimated 82 diseases in the Orphanet database¹⁵⁴.

National alliances of patient organisations and patient representation

There is currently no national alliance for rare disease patient organisations in Estonia. There are only a few non-profit patients associations in the field of rare diseases (Estonian Spinal Hernia and Hydrocephalus Association, Estonian Cystic Fibrosis Society, Estonian Phenylketonuria Society, Estonian Haemophilia Society, Estonian Prader-Willi syndrome Society), who are also members of *Eesti Puuetega Inimeste Koda* (The Estonian Chamber of Disabled People). Support for patient organisations is provided by The Estonian Chamber of

¹⁵¹ <http://www.kliinikum.ee/geneetikakeskus/>

¹⁵² See the regularly updated list in Estonian for further information: <http://www.kliinikum.ee/geneetikakeskus/>

¹⁵³ http://www.coe.int/t/dg3/healthbioethic/Activities/07_Human_genetics_en/Brochure/default_en.asp

¹⁵⁴ Information extracted from the Orphanet database (December 2012).

Disabled People and *Eesti Patsientide Esindusühing* (The Estonian Patient Advocacy Association (EPAA)). EPAA is a non-profit NGO established in 1994, with the primary aim of advocating for human and civil rights of health and social care service users. The activity of EPAA is financed as purpose-oriented grants from a state budget. In addition there are possibilities to use funds from the gambling tax for project-based financing for patients' organisations. Patient organisations are represented on the council of the Estonian Health Insurance Fund and grants are available for patient organisations to attend these meetings.

Sources of information on rare diseases and national help lines

Orphanet activities in Estonia

Since 2004, there is a dedicated Orphanet team in Estonia, currently funded by the Department of Paediatrics at the University of Tartu. The team was designated as the Orphanet team for Estonia by the Ministry of Social Affairs in 2010 to which an application was made in 2012 for future funding. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. In 2011 the Orphanet Estonia national website¹⁵⁵, in Estonian, was launched by the Orphanet Estonia team.

Official information centre for rare diseases

There is no official information centre for rare diseases in Estonia other than Orphanet.

Help line

There is currently no help line for rare diseases.

Other sources of information

The Agrenska Foundation provides additional information on rare diseases.

Good practice guidelines

No specific information reported.

Training and education initiatives

There are special advanced courses for physicians (2-3 courses per year) on rare disorders, aimed at improving the early detection and diagnosis of certain rare diseases (Prader-Willi syndrome, Angelmann syndrome, SMA, Dravet Syndrome, etc) organised by the Department of Continuing Education at Tartu Medical University. In 2009 -2011 the number of advanced courses on rare disorders organised by the Department of Continuing Education at the Tartu Medical University increased, due to rising interest in the subject. This activity is also planned for the future and a new course was held in 2012.

National rare disease events in 2012

Due to Estonia's small size, there are no special annual rare disease events, nonetheless rare diseases are given a spotlight during the annual meetings of the Estonian Society of Human Genetics and Estonian Society of Laboratory Medicine.

In August 2012 a meeting "Orphan diseases – today and future" was organised by Agrenska Estonia in Tammistu, Tartumaa, with more than 160 participants from different areas (doctors, nurses, physiotherapists, teachers, patients, social workers, etc).

Hosted rare disease events in 2012

No events reported in *OrphaNews Europe*.

Research activities and E-Rare partnership

National research activities

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, *Eesti Teadusfond* (Estonian Science Foundation) supports research on rare diseases at national level on the basis of appropriate applications, but there is no distinction from other projects not related to rare diseases (approximately 40,000-65,000 EUR

¹⁵⁵ <http://www.orpha.net/national/EE-ET/index/avaieht/>

available over four years)¹⁵⁶. Some projects that involve research on rare diseases are financed by Targeted Financing from the Estonian Government (dysmorphic syndromes, methylation defects such as Prader-Willi, Silver-Russell and Beckwith-Wiedemann syndrome, metabolic diseases such as phenylketonuria, classical galactosemia, mucopolysaccharidoses, fatty acid oxidation defects and mitochondrial diseases, and congenital adrenal hyperplasia).

Participation in European research projects

Estonian teams participate, or participated, in European rare disease research projects, including: AAVEYE, EURAPS, MOLDIAG-PACA and RD PLATFORM. Estonia contributes to the EURO-WABB registry project.

E-Rare

Estonia is not currently a partner of the E-Rare consortium.

IRDiRC

Estonian funding agencies have not yet committed national funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

There is currently no orphan medicinal product committee in Estonia. On the sphere of drugs the main adviser is the Drug Committee. The main objective of the Drug Committee is to advise the Ministry of Social Affairs on the positive list of reimbursement medicines and to debate about the use of pharmaceuticals and about the need to update the reimbursement rules for some product or group of products. Orphan medicinal products are subject to Drug Committee on the same basis as other medicines.

Orphan medicinal product incentives

There are no specific incentives for orphan medicinal products in Estonia.

Orphan medicinal product market availability situation

In theory, all orphan medicinal products with EU market authorisation can be bought in Estonia. All information concerning drugs, including orphan medicinal products is available in Ravimiamet¹⁵⁷ (*Stage Agency of Medicine of Estonia*).

Orphan medicinal product pricing policy

There is no specific pricing policy for orphan medicinal products in Estonia.

Orphan medicinal product reimbursement policy

There is no concrete list of orphan medicines for reimbursement and no specific programmes to facilitate the provision of medicines to rare disease patients. Reimbursement of the cost of medicines to patients comes from joint medical-insurance funds on the basis of *Eesti Haigekassa's* (Estonian Health Insurance Fund) medicine reimbursement budget in accordance with the diagnosis, where the criterion for establishing the selection of corresponding diagnoses is not so much the incidence of the disease as its seriousness and mortality, the possibility of an epidemic, the need for alleviating the associated pain or other humane considerations, the chronic nature of the disease together with the impairment caused to the quality of life, and the match with the financial possibilities of the medical insurance scheme. Children under the age of 4 are entitled to 100% drug reimbursement. Rare diseases are also included in the catalogue of described diagnoses for reimbursement. Currently¹⁵⁸ *Haigekassa* reimburses patients 100% of the costs of 20 orphan medicinal products.

Mostly orphan drugs that are reimbursed by Estonian Health Insurance Fund (EHIF) or other funds (e.g. charity funds) are available in Estonia. EHIF reimburses orphan drugs like Busilvex, Exjade, Kuvan, Nexavar, Nplate, Revatio, Revlimid, Sprycel, Tasigna, Thalidomide, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Xaluprine, Zavesca. Also many drugs without orphan designation are reimbursed, like Fabrazyme, Revolade, Replagal, Glivec, Alimta, Ammonaps, Avastin, Filgrastim, Cancidas, Cerezyme, Vfend etc.

¹⁵⁶ This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p 11)

¹⁵⁷ <http://www.sam.ee/>

¹⁵⁸ Information accurate in December 2011.

Due to the high cost of these orphan medicinal products, only those which are reimbursed by *Eesti Haigekassa* (Estonian Health Insurance Fund) are easily accessible. Patients can access all other orphan medicinal products if they are willing to pay the cost of the drug.

Other initiatives to improve access to orphan medicinal products

There are no specific programmes to facilitate the provision of medicines to rare disease patients, however the Estonian Health Insurance Fund has previously reimbursed off-label drugs for rare diseases.

Other therapies for rare diseases

The Estonian Health Insurance Fund has reimbursed medical food if used for rare diseases.

Orphan devices

No specific information reported.

Specialised social services

The Estonian Agrenska Foundation, founded by several sources including Agrenska Sweden, the University of Tartu, the Estonian Board of Disabled People, the Tartu University Hospital Foundation, and *Stenstroms Skjortfabrik Eesti* provides counselling and care for families with children with rare disorders. Like its Swedish counterpart, the Estonian Agrenska Foundation¹⁵⁹ targets the family, offering a family-centred counselling system that should be able to cover all of Estonia in the coming future. The service focuses on families of children with disabilities, offering psychosocial, educational and medical information and support. In 2012, several respite camps were organized by the Estonian Agrenska Foundation. The reimbursement of these services varies from full reimbursement to partial payment by patients. Every family with a disabled child is entitled to a fixed sum per year from the government for respite care services. The Maarja Village Foundation (founded by the Tartu Toome Rotary Club) runs a residential centre which accommodates up to 33 young people with mental disabilities. Therapeutic recreational programmes exist for certain rare diseases (Prader Willi for example) and are provided by patient organisations and are partially reimbursed. Services exist to promote the integration of patients with disabilities in schools and in the work place and are financed by the government.

1.8. FINLAND

Definition of a rare disease

There is no official definition for rare diseases in Finland. At present the parties involved in the field of rare diseases normally use the common EU definition of no more than 5 in 10 000 individuals. In matters concerning orphan medicinal products Finland officially applies the same definition used in European Regulation on Orphan Medicinal Products. Finland has decided (for the draft plan) to use the EU definition of no more than 1 in 2000 and severe/debilitating diseases.

National plan/strategy for rare diseases and related actions

There is currently no national plan/strategy for rare diseases, though the first steps have been taken in the process. Funding specifically focused on national plan related activities was applied for in late 2011 from the Ministry of Social Affairs and Health (this was accepted in 2012). A national advisory committee and a pilot have been appointed for the elaboration of the plan. During 2011 a nationwide survey was performed to identify centres who consider themselves as experts related to a rare disease or disease group. The Ministry of Social Affairs and Health decided to invite stakeholders in the field to become members of the steering committee, including hospital districts, governmental institutes like the National Institute for Health and Welfare, Väestöliitto, the Orphanet National Advisory Board, the umbrella organisation for rare diseases HARSO, Helsinki University Hospital, and the Harvinaiset Network for Rare Diseases to name representatives for a steering committee for elaborating the national plan. There will be a focus on establishing centres of expertise, with a step which will include patients before they reach the centres (i.e. early health care pathways to diagnostic processes). However, a healthcare reform is underway which may slow down the work on the

¹⁵⁹ <http://www.agrenska.ee/>

plan. A meeting is planned in March 2013 to advance with the elaboration of the plan. The aim is to have the plan ready during 2013, the designation of expert centres will be a much longer process to follow.

Current expenditures for rare diseases fall within the general health system budget with additional ad hoc funding on the basis of rare disease projects.

Finland participated in a project (which ran from 2009 to 2010) focusing on cooperation possibilities between Nordic countries in the field of rare diseases. The project was supported by the Nordic Council of Ministers, and was entitled "*Kartläggning av möjliga nordiska samarbetsområden anknutna till små och sällsynta diagnosgrupper*" ("Report on possibilities for co-operation between the rare disease groups in Nordic Countries"). The goal of the project is to create recommendations for Nordic cooperation in all fields: medical, social, psychological and pedagogical. The project came to the conclusion¹⁶⁰ that co-operation with the Nordic countries should involve continuous exchange of experiences and knowledge of rare diseases through regular conferences and seminars, increasing co-operation with small separate projects in the field of rare diseases, and joint Nordic training in the field.

Planning is also underway for a national plan for cancer treatment and research with the hope that the process for the rare disease and cancer plans to feed into one another.

Centres of expertise

There are currently no official centres of expertise for rare diseases in Finland. However, the departments for different medical specialities in university hospitals act as reference centres for rare diseases, and certain university hospitals specialise in specific rare operations related to rare diseases, such as congenital heart defects, cleft lip or palate, craniofacial malformations, glaucoma, retinoblastoma and biliary atresia according to the decree of the Ministry of Social Affairs and Health (767/2006) based on a law for specialised medical treatment (1062/1989).

The establishment of centres of expertise and healthcare pathways will be one of the first topics to be dealt with in the elaboration of a national plan for rare diseases, with hope for the first official centres of expertise by 2013. There are already officially designated expert centres, though not for specific diagnoses but for specific treatments (craniofacial surgery, childhood rheumatoid arthritis, hematologic malignancies in children).

The Ministry of Social Affairs and Health carried out a nationwide survey in 2011 to identify unofficial centres of expertise which fueled discussions on the subject at the 2012 meeting of the Orphanet Scientific Advisory Board.

Registries

In general, all the main health care registries are under the National Institute for Health and Welfare, for example Hospital Discharge Registry, Cancer Registry, Malformation Registry and Birth Registry. There is a need for new legislation related to registries; this is in the pipeline in the Ministry of Social Affairs and Health. Finland has not decided how to approach the question of rare disease registries, this will be part of the national plan. The other registries are financed by the government.

There are two legally specified registries concerning rare diseases: the Finnish register of congenital anomalies and the Finnish register of visual impairment. However, there is no designation process for rare disease registries.

The Finnish Haematology Registry and Clinical Biobank was established in 2010 by the Finnish Association of Haematology (FAH). In addition, rare inherited cancers are included in the Cancer Register and rare kidney diseases are included in the Finnish registry for Kidney Diseases. There is a national registry for primary and specialised health care¹⁶¹) but in this registry rare diseases are difficult to trace due to the problems of ICD10. Finland contributes to European registries including TREAT-NMD and EUROCAT.

Neonatal screening policy

All newborns are screened for hypothyroidism but not for phenylketonuria as it is practically absent in the Finnish population. A pilot scheme for screening additional metabolic diseases including congenital adrenal hyperplasia (CAH), MCAD deficiency, LCHAD deficiency, Glutaricaciduria type 1 (GA1), and phenylketonuria was started in 2007 in the Turku area, concerning around 3000 newborns per year. No decision has at present been made concerning the continuation of the pilot beyond the year 2012 or widening of the pilot to other areas in Finland, though experts representing university hospitals now suggest that screening for newborn congenital

¹⁶⁰ <http://www.nordicwelfare.org/filearchive/1/119089/Rapport%20med%20bilagor%20final.pdf>

¹⁶¹ www.thl.fi/tietokantaraportit

metabolic diseases should be widened in 2015, so that the screening practice in Finland would be similar to other western countries. A screening recommendation was handed over to the Ministry of Social Affairs and Health in 2012. In addition to this, hospitals organise screening for phenylketonuria in newborns of non-Finnish origin.

Genetic testing

Genetic testing on the national level is not centrally organised but has developed partly based on needs for certain tests but partly due to local desire to have a molecular laboratory also for training/educational purposes. There are laboratories offering selections of tests (especially the founder mutations of the so called Finnish Disease Heritage) in University Hospitals, the largest in Helsinki. Genetic tests are performed in all five University towns either in the University (Turku) or in the University Hospital or a linked state-owned laboratory company (Helsinki, Kuopio, Oulu, and Tampere).

In addition, there is one major private laboratory offering testing, also to public health care.

There are no national guidelines, but most of predictive testing (including familial cancer) happens in genetic clinics. According to the law on the patient's status and rights (1992/785) informed consent is always sought for medical tests but it does not have to be written. Clinical geneticists have agreed among themselves that tests for adult-onset diseases or carriership are not performed in minors. Most physicians representing other specialties agree to this principle. Some of the laboratories are accredited, some are still in the process of being accredited but they all belong to larger laboratory units which are, at least partly, accredited.

Tests are part of the hospital fee of which the patients pay a nominal sum. The municipalities then are responsible for paying for the tests: the rest is paid by the municipalities. It is rather rare that the payment would create a problem: usually if the physician in charge of diagnosis/treatment of a patient suggests genetic test(s), they are always paid without any discussion.

Genetic testing abroad creates usually no problems, many even quite common diseases like NF1, Marfan and related disorders etc are regularly bought elsewhere, from Europe or the USA.. Then, usually, a laboratory that performs the required test is sought for from Orphanet. Also Finnish laboratories carry out genetic tests for foreign customers, especially in case of the diseases of the so called Finnish Diseases Heritage.

Diagnostic tests are registered as available in Finland for 182 genes and an estimated 230 diseases in the Orphanet database¹⁶². Other tests are available abroad.

National alliances of patient organisations and patient representation

Representatives of patient associations decided to set up a national alliance at their meeting at the Family Federation Finland, in Helsinki on 6 June 2011. During this meeting it was decided to set up a work group, led by Elina Nykyri, head of the Finnish Turner Association, to prepare a constitutive meeting held on 8 October 2011. A first statutory meeting was held on 21 January 2012. The new alliance, named HARSO, HARvinainen (rare) Sairauksien (diseases) Organisaatio (organisation) welcomes all Finnish patient organisations that represent one or more rare diseases or disabilities. Harso is run by patients themselves. There were 29 organisations out of a total of 51 in Finland present at the launch of the association. The new umbrella group will advocate for the rare disease patients, their families and their organisations in Finland, aiming for the best possible health and social care for the entire rare disease community. One of the main objectives will be to raise awareness of rare diseases and disabilities in order to facilitate diagnosis. Rare diseases and/or disabilities affect the daily lives of approximately 250 000 people in Finland. Harso will provide the rare disease community with strength in numbers for the first time. The organisation unites the rare disease community, creating a common voice and more visibility. So far, some rare disease organisations have chosen to stay outside Harso.

At present, individual patient organisations may be consulted on their opinion about forthcoming legislation, but the bodies to be consulted on such matters have not been defined. The Ministry of Social Affairs and Health has a council of the disabled which represents all groups of the disabled including rare disease patients.

Sources of information on rare diseases and national help lines

Orphanet activities in Finland

Since 2004 there is a dedicated Orphanet team in Finland, previously hosted by the Medical Genetics Clinic of Vaestoliitto, the Family Federation of Finland, and now hosted by the Norio-centre. The team was designated as the Finnish national Orphanet team by the Ministry of Social Affairs and Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing

¹⁶² Information extracted from the Orphanet database (December 2012).

research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database, as well as maintaining the Orphanet Finland national website¹⁶³ in Finnish.

Orphanet and Terveysportti¹⁶⁴ have established a collaboration to add links from Terveysportti's Finnish texts to the relevant Orphanet disease page were added: Orphanet is thus included in Terveysportti's searches for these 300 "most common rare diseases" and will make Orphanet better known amongst Finnish healthcare professionals. Terveysportti is maintained by Duodecim, the Finnish Medical Society, a scientific society adhered to by almost 90% of Finnish doctors and medical students. The Terveysportti portal is for healthcare professionals and is used nationwide in public health care units, hospitals, private practices and pharmacies as well as the universities' medical faculties. The service consists of more than 35 databases and helps professionals find day-to-day medical information quickly and reliably from one source.

Official information centre for rare diseases

There is no official information centre for rare diseases in Finland other than the services provided by Orphanet, however the Norio-centre serves unofficially this function for health care providers, students, teachers, parents etc.

Help line

There is no official help line for rare diseases. The Norio-centre has a nationwide phone and e-mail service for matters concerning rare diseases, which operates on work-days: the Norio-centre receives part of its funding from Finland's Slot Machine Association (RAY). The main purpose of RAY is to raise funds through gaming operations to promote Finnish health and welfare.

Other sources of information

Established in 1993, the Harvinaiset Network is a network of 18 non-governmental, non-profit organisations funded by RAY, Finland's Slot Machine Association. The members of the network have signed a partnership agreement and are regarded as equal partners in the network.

The Network provides information on rare diseases and services, raises awareness of the needs of people with rare diseases and organises courses for patients and their families. Harvinaiset also maintains an internet portal with information about rare diseases in Finnish. An updated website was launched in 2010 as well as a web based service to help individuals without patient organisations for their disease to find other individuals with the same rare disease. The Harvinaiset network also participates in the maintaining of the Nordic website www.rarelink.fi.

Most providers of services for rare diseases also have web-based information and phone or web answering services: they provide general information about diseases, contacts for treatment, advocacy, rehabilitation, psychological support and support from patient organisations or peer support groups.

Good practice guidelines

Finland has a strong tradition of producing best practice guidelines. They, however, are written based on Cochrane reviews and as this is not possible in case of rare diseases, and such guidelines have not been produced. Health care personnel in Finland, especially medical doctors, have no difficulties in accessing and using guidelines written in English.

Information on 35 monogenic diseases belonging to the Finnish Disease Heritage¹⁶⁵ can be found at a database findis.org. For each disease, the prevalence or incidence and a short description of clinical symptoms are provided, as well as genetic locus and a molecular description for identified mutations. As the character and consequences of all known mutations, Finnish and foreign, are described at the DNA and polypeptide level and disease allele frequencies reported for Finnish mutations, the database can be used as a best practice guideline for molecular diagnostics of these diseases. However, this database does not provide guidelines or information related to treatment or follow up of these diseases.

The database follows the Quality Criteria for Health Related Websites recommended by the European Commission: funding for the database has been provided by the Academy of Finland, Centre of Excellence in Disease Genetics.

¹⁶³ <http://www.orpha.net/national/FI-FI/index/kotisivu/>

¹⁶⁴ <http://www.terveysportti.fi/>

¹⁶⁵ <http://www.findis.org/main.php?action=disease>

Training and education initiatives

There are regular “dysmorphology afternoons” twice a year, especially planned to support young doctors in training.

National rare disease events in 2012

International Rare Disease Day 2012 was coordinated by The Finnish Network for Rare Diseases, Harvinaiset-verkosto. Together with the patient organisations the Network organised a webinar entitled “Rare Disease Day 2012” at the Finnish Parliament Annex, called the Little Parliament on 29 February 2012. Ms. Paula Risikko, The Minister of Social Affairs and Health as a guest speaker. Dr Päivi Kaukonen, Ministerial Adviser from the Ministry of Social Affairs and Health, presented survey which has been carried out among university and central hospital chief physicians and Harvinaiset Network member organisations of diagnostics, care and rehabilitation with rare disease patients in Finland. Dr. Kaukonen announced the establishment for April 2012 of a steering group for the preparation of the national plan by the Ministry. The seminar was also an opportunity to hear the results of the Harvinaiset survey launched in January 2012 on rare diseases which received around 700 responses.

Swedish Orphan Biovitrum Finland organised the 4th *Harvinaiset Sairaudet-päivä* (Rare Disease Day) together with stakeholders in Helsinki on 19 October 2012. This day provided a forum for questions concerning research and management for Finnish decision-makers and specialists. The principal goal of the day was to discuss how Finland would become a model country for rare disease research and management and which actions would ensure that patients suffering from rare conditions would be entitled to the same quality of treatment as other patients.

Hosted rare disease events in 2012

No specific information reported.

Research activities and E-Rare partnership

National research activities

There are no specific programmes for rare disease research and projects compete with other topics in the calls of Finnish Academy and various foundations. Fundraising events do not belong to the research funding traditions in Finland, except for the research related to cancer and paediatric diseases.

Research in the field of rare disease has been focused on diseases of so-called Finnish Disease Heritage; nearly 40 rare inherited diseases are over-represented in Finland in comparison to other populations. Most of the genes associated with these diseases have been mapped and cloned in Finland during the last 20 years. Also rare forms/founder mutations amongst more common ones, like hereditary nonpolyposis colorectal cancer (HNPCC), hereditary connective tissue diseases, and long QT syndrome, have been studied.

Many different bodies fund medical research programmes in Finland. There are no specific programmes for research of rare diseases, which compete with more common diseases for the funds. Part of this funding for research goes towards research on orphan medicinal products. Five universities with medical faculties have programmes of their own, which are partly funded by a special State contribution (EVO). The Finnish Academy and private foundations finance substantially medical research and some rare disease research programmes amongst others.

Participation in European research projects

Finland participates, or has participated, in European rare disease research projects including: BNE, CLINIGENE, DEMCHILD, EUGINDAT, EUMITOCOMBAT, EURAPS, EUREGENE, EURO BONET, EURO GENTEST 1 & 2, EUROPEAN LEUKEMIA NET, GRIP, GEN2PHEN, LYMPHANGIOGENOMICS, NEUROPRION, PEROXISOMES, PROTHETS, INTERPREGEN, INTREALL, PULMOTENSION, TREAT-NMD and RD PLATFORM.

E-Rare

Finland is not currently a partner of the E-Rare consortium.

IRDiRC

Finnish funding agencies are not yet committed members of the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

No specific information reported.

Orphan medicinal product incentives¹⁶⁶

The Finnish Medicines Agency (*Fimea*, which before the 1st November 2009 was known as the National Agency for Medicines *Lääkelaitos*) gives free administrative and scientific advice to bodies developing orphan medicinal products. Furthermore, the special status of orphan medicinal products has been taken into account in inspection and authorisation procedures. *Fimea* also maintains a registry of clinical trials.

The evaluation criteria are the same for all medicinal products; no exceptions for orphan medicinal products are stated in the Health Insurance Act. However, the health economic evaluation is not always required from the marketing authorisation holder of orphan medicinal product if justified by the applicant.

Orphan medicinal product market availability situation

Of the orphan medicinal products with EU market authorisation, 51 are available on the market currently in Finland in at least one form, if not in all forms. The *Fimea*¹⁶⁷ lists the following orphan medicinal products as available on the market in Finland: Adcetris, Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Elaprase, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyf, Firdapse, Gliolan, Increlex, Inovelon, Jakavi, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedea, Prialt, Revatio, Revlimid, Revolade, Savene, Signifor, Soliris, Somaver, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Xagrid, Yondelis, Zavesca.

Orphan medicinal product pricing policy

According to the 2005 *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹⁶⁸ in the section concerning Finland, "A reasonable wholesale price refers to the maximum price at which the product may be sold to pharmacies and hospitals. The holder of marketing authorisation must be able to justify the reasonableness of the proposed wholesale price for a medicinal product that is to serve as a basis for the reimbursement payments. The application must include a detailed, comprehensive assessment of the cost of the drug therapy and the benefits expected to be gained thereby. Moreover, the application must include an evaluation of the product in relation to alternative drug treatments and other therapies. The application must also include the validity period of the pharmaceutical patent or a supplementary protection certificate, an estimate of the sales volume and number of users of the product over the next three years as well as the approved price and ground for reimbursement of the product in other EEA countries.

"Applications concerning medicinal products containing a new active substance must contain a health economic evaluation. When considering the reasonableness of the proposed wholesale price, the Pharmaceuticals Pricing Board takes into account the cost of the drug therapy and the benefits to be gained from its use as regards both the patient and the overall health care and social costs. The Pricing Board will also consider the cost of the treatment alternatives, the prices of comparable medicinal products and the price of the medicine in question in other EEA countries. Manufacturing, research and development costs are also taken into consideration when making a decision on application, if they are considered relevant by the applicant, as are the funds allocated for reimbursement payments."

Orphan medicinal product reimbursement policy

All medicines with a wholesale price approved by the Pharmaceuticals Pricing Board are automatically entitled to reimbursement under the basic refund category. The basic reimbursement is currently 35% of the purchasing price. In certain diseases or conditions, lower (65%) or higher (100%) special reimbursement is available.

In October 2010 Harvinaiset, the Finnish Network for Rare Diseases, sent a letter¹⁶⁹ to the Ministry of Social Affairs and Health concerning the reimbursement of orphan medicinal products in Finland in order to expose the need for an improved approach to the issue especially for Fabry disease, Myasthenia gravis and Long QT syndrome. The Ministry wrote back to assure that the pharmaceutical policy foreseen for 2020 would deal with many of the concerns raised by the network including the development of medications towards more specific treatments (including orphan medicinal products), price regulations, updating the list of diseases for

¹⁶⁶ This section was written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp11-12)

¹⁶⁷ <http://www.fimea.fi/medicines/fimeaweb>

¹⁶⁸ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p12)

¹⁶⁹ http://harvinaiset.fi/ajankohtaista/stm-n-vastaus-kannanottoon-laeaekehoidon-korvauksista&rurl=translate.google.fr&twu=1&usg=ALkJrh-90epLiXoahxcmk5V47DH0lr_Av

which reimbursement is provided through the Government Regulation in place, uniform payments and payment caps for social and health care.

Other initiatives to improve access to orphan medicinal products

No specific information reported.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Respite care services are available and local authorities are responsible for their provision, but some are equally provided by private institutions: patients and families often have to provide co-payment. Therapeutic recreational programmes are available under different forms and patients have to partially pay for these services though some funding can be provided by RAY. Services for transport, modifications for housing arrangements, day-care, interpreter (sign language etc), personal assistants etc are available for those with handicaps by local authorities, provided for by the law 380/1987 in 1987 (updated 1267/2008 and 981/2008).

Patients with a rare disease, as well as all others with a severe disability, were given new possibilities 2009. The legislation for personal assistance was updated as of 1 September 2009. This update follows the principles of Independent Living Movement. Personal assistance for persons with a severe functional disability is free of charge. Besides the support in the daily living, work and education this now also includes assistance with participation in recreational activities, social activities and education. The service is financed by the municipalities.

1.9. FRANCE

Definition of a rare disease

Stakeholders in France accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 people.

National plan/strategy for rare diseases and related actions

First French National Plan for Rare Diseases 2005-2008

France was the first EU country to set up a comprehensive rare disease plan in 2004 for the period 2005-2008 with allocated funding. This first plan, subtitled "Ensuring equity in the access to diagnosis, treatment and provision of care", included 10 objectives:

- Increase knowledge of the epidemiology of rare diseases;
- Recognise the specificity of rare diseases;
- Develop information on rare diseases for patients, health professionals and the general public;
- Train health professionals to better identify rare diseases;
- Organise screening and access to diagnostic tests;
- Improve access to treatment and quality of healthcare provision for patients;
- Continue efforts in favour of orphan medicinal products;
- Respond to the specific needs of accompaniment of patients suffering from a rare disease and develop support for patients' organisations;
- Promote research and innovation on rare diseases, in particular on treatments;
- Develop national and European partnerships in the domain of rare diseases.

The first national plan provided for the official recognition, funding and evaluation of 131 centres of expertise, called "*centre de référence maladies rares*" in France ("Reference Centres"). This national network was completed in 2008 by the recognition of a second level network of 500 centres working in close connection with the Reference Centres. They are called "*centre de compétences maladies rares*" ("Competence Centres"),

and are the equivalent of regional centres of expertise; they received no specific funding. New rare disease research networks and research projects were supported by a national call for proposals. Information on rare diseases, orphan medicinal products and related fields was developed by Orphanet (established in 1997, but whose budget was increased significantly thanks to the plan). A national helpline for patients (called “*Maladies Rares Info Services*”¹⁷⁰, French “Rare Disease Information Service Helpline”) was developed. Several new information products for health professionals were developed such as emergency guidelines, developed by Orphanet, and specific clinical practice guidelines (called “*protocole national de diagnostic et de soins*” – PNDS – “*national diagnosis and treatment protocol for a rare disease*”), developed by the Reference Centres; all these guidelines are published on the Orphanet website. Emergency cards to be used by the patients if necessary were also developed by the French Ministry of Health.

Funding for this first national plan was provided within the general health system budget with ad hoc funding on the basis of rare disease projects (over €100 million for the duration of the plan).

Evaluation of the first plan

The first French National Plan for Rare Diseases underwent intense scrutiny when its four-year term ended in 2008. The main goal of the evaluation was to provide data to serve for the elaboration of a second national plan, initially expected in 2010. An Evaluation Committee consisting of health, economics and sociology experts, under the authority of the French Council for Public Health, measured the initial objectives of the plan against the corresponding actions undertaken during the four years of the plan. The official evaluation report was rendered to the French Minister of Health in May 2009. The document provided an analysis of the accomplishments, advances, and shortcomings of each of the ten objectives of the plan. A series of propositions and recommendations for the elaboration of a second plan was also provided.

Throughout the evaluation, the Evaluation Committee underscored the satisfaction of the different stakeholders towards the overall results of the plan. The objectives judged most pertinent – access to information (Orphanet and *Maladies Rares Info Service*), new healthcare organisation (Reference Centres), research funding, orphan product accessibility, and partnerships with European institutions – have benefited from corresponding actions that have satisfactorily fulfilled the planned goals. The need to strengthen these successful actions was underlined in the evaluation. However, some objectives – specifically those concerning epidemiology, professional training for rare diseases, and screening and diagnostic programmes – were considered insufficiently developed. The strategies to meet these goals needed to be reformulated taking stock of the difficulties encountered and planning actions to overcome obstacles.

The tenth objective of the plan, “Develop national and European partnerships in the field of rare diseases”, received an overall favourable evaluation with propositions formulated to enhance and encourage European collaboration. Furthermore, the Evaluation Committee proposed the development of measures to bring non-European industrialised and developing countries into the fold. Indeed, throughout the evaluation of the plan, the necessity for European and international-level coordination and resource-sharing was emphasised.

The Evaluation Committee’s report¹⁷¹ was completed by a self-assessment report¹⁷² drawn up by the Steering Committee of the plan within the Ministry of Health. These two reports and the testimonies of rare disease health professional, industry and patients’ organisation stakeholders who had contributed to the first plan were presented and discussed at the final meeting of the Follow-up Committee of the plan.

On 30 September 2010, the French Alliance for Rare Diseases (“*Alliance Maladies Rares*”), in collaboration with EURORDIS, organised a national conference on rare diseases¹⁷³ in the context of the Europlan project. The theme of the conference was “The French plan in the European landscape”. This conference gathered a large range of stakeholders and focused on lessons drawn from the first plan for the benefit of other European countries.

Second French National Plan for Rare Diseases 2011-2014

The second French National Plan for Rare Diseases¹⁷⁴ was elaborated during 2009-2010 by the Ministry of Health with the collaboration of the Ministry of Higher Education and Research from the results of the evaluation of the first plan and from the conclusions of seven working groups, which had gathered during 34

¹⁷⁰ <http://www.maladiesraresinfo.org>

¹⁷¹ http://www.hcsp.fr/docs/pdf/avisrapports/hcspr20090317_maladiesRares.pdf

¹⁷² http://www.sante.gouv.fr/IMG/pdf/Evaluation_interne_Plan_National_Maladies_Rares_2005-2008.pdf

¹⁷³ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_france_europlan.pdf

¹⁷⁴ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

meetings 184 representatives of health professionals, rare disease experts, researchers, patients' organisations and administration. The second plan was launched on 28 February 2011 on the occasion of Rare Disease Day, with a budget of €180 million for the period 2011-2014. The ten objectives of the first plan have been consolidated into three main objectives:

- Improve the quality of care for rare disease patients;
- Develop research on rare diseases;
- Amplify European and international cooperation in the field of rare diseases.

These three objectives encompass actions such as:

- Quality assessment and networking of the existing French Reference Centres;
- Improvement of access to genetic diagnosis;
- Development of neonatal screening of rare diseases;
- Proper use and facilitated access to drugs, orphan medicinal products and any other medical product necessary for the patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

The second plan includes 15 measures and 47 specific actions. The key measures of the plan are:

- Creation of a Foundation for Scientific Cooperation on Rare Diseases (called the "*Fondation maladies rares*"¹⁷⁵) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Disease Database (called "*Banque nationale de données maladies rares*" - BNDMR) to allow mapping of patients' needs and delivered healthcare, and to facilitate their recruitment for clinical and epidemiological studies and clinical trials. The national registry BNDMR will be based on the collection of a minimum data set, common to all patients and rare diseases and all the reference and regional centres;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature for the patients' follow-up;
- Access to next-generation sequencing (NGS) technology for genetic diagnosis. Most of the French academic laboratories will be equipped at the end of the second year of the plan with NGS facilities to optimise genetic diagnosis of a large set of rare diseases. Various levels of NGS will be implemented during the plan for speeding up and maximal diagnosis coverage;
- Restructuring of rare disease reference and regional centers into a limited number (around twenty) of coherent "national clinical networks" (called "*filières de santé maladies rares*"), gathering all rare disease relevant stakeholders and centered on a homogeneous group of rare diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up. These future French clinical networks should be connected to the future European Reference Networks (ERN) concerning rare diseases.

The additional actions foreseen in the plan to improve the quality of care are:

- Creation of a "permanent working group" for the monitoring of Reference Centres and the future national clinical networks;
- Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed out of their marketing authorisation;
- Enhancement of rare disease clinical practice guidelines ("PNDS") development;
- Training of medical doctors and paramedical professionals;
- Better coordination of health care and social care;
- Improvement of information for rare disease patients supporting Orphanet and *Maladies Rares Info Service* and the creation of a European unique number for rare disease help lines.

The implementation and the follow-up of the plan is the mission of a dedicated Steering Committee (called "*Comité de suivi et de prospective*" – Follow-up and Prospective Committee) which held its first meeting on 19 May 2011 and meets at least once a year. This committee is chaired by the General Director for Provision of Healthcare in the French Ministry of Health. Five thematic working groups reporting to the Steering Committee were established to help implement the plan. They include a "permanent working group", dedicated at first to the definition of a new evaluation process of the Reference Centres, and later to the monitoring of Reference Centres and their future national clinical networks, as well as four temporary working groups: one dedicated to defining the specifications, scope and organisation of the future national clinical

¹⁷⁵ The "*Fondation maladies rares*" was created on 6 February and launched officially on 29 February 2012: <http://www.fondation-maladiesrares.org>

networks, one to help improve the quality of information and healthcare, one to develop the access to NGS, and the last one to help develop the National Rare Disease Database. The Steering Committee is in charge of the follow up of the plan, its implementation according to schedule, the effective involvement of relevant bodies and institutes, as well as the survey of new methods for diagnosis, prevention, treatment and care for rare disease patients which would justify the adaptation of the plan during its progress.

Since 1 December 2012, hospitals – in priority Reference Centres – began one of the key actions of the second plan: coding in the National Database of Inpatient Registrations (“PMSI”) all hospitalised rare disease patients using systematically Orphanet nomenclature. The goal is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways.

An “information and experience sharing meeting” was organised on 19 December 2012 concerning the implementation of the Second Plan for over 300 participants, in particular for all the coordinators of the Reference Centres. The meeting objectives were to share information with the coordinators on the progress of the plan. In particular the new evaluation procedures for Reference Centres were presented and discussed, as were the future national clinical network organisation and the new method to develop “PNDS” (*See section on Good Practice Guidelines*).

Second French National Plan for Cancers (including rare cancers) 2009-2013

A second National Plan for Cancers¹⁷⁶ was launched on 2 November 2009 for the period 2009-2013. This plan is the continuation of the first national plan¹⁷⁷ which covered the period 2003-2007, during which pilot projects targeting an organisation of expert centres for rare cancer patients were supported. The six main domains concerned by the plan are: research, observation, prevention, screening, care, and “living with and after cancer”. A specific action of the plan is dedicated to the development of specialised expert centres for rare cancer patients, labelled “reference centres for rare cancers”. The term “rare cancers” applies to the following cancers: those which are diagnosed in fewer than 3/100 000 persons per year; or those requiring highly specialised management, owing to their unusual location, or to their occurrence at a specific or complex site.

The National Cancer Institute (“*Institut national du cancer*” – *INCa*) published a report entitled “The Situation of Cancer in France in 2011”. This report gives an overview of the measures in place for cancers, including rare cancers, and gives key facts and figures concerning the cancer patients in France. It was published at the same time on the INCa site and on a new web portal on cancer data¹⁷⁸. The INCa also released at the end of 2011 a first report on the expertise activity for rare adult cancers, including updates on organisation, collaborations, translational research and clinical trials, survey of cases in national databases, and elaboration of recommendations amongst other actions¹⁷⁹. A second report concerning the activity of the “Expert Centres” was published in 2012¹⁸⁰, as well as a document published in French¹⁸¹ and in English¹⁸² describing this specific organisation.

The INCa published two new reports on genetic testing and treatment for hereditary cancers in 2012. The first one summarises the 2011 activities of French oncogenetic platforms. The second one focuses on molecular genetic testing for targeted therapies in France in 2012¹⁸³.

French National Plan for Rare Disabilities 2009-2013

A plan aimed at rare disabilities (of which rare diseases may be a cause) was adopted on 27 October 2009 for the period 2009-2013¹⁸⁴. The National Solidarity Fund for Autonomy (“*Caisse nationale de solidarité pour l’autonomie*” – CNSA - in charge of funding for the autonomy of the elderly and disabled people) is in charge of its implementation. A “rare disability” is a French notion¹⁸⁵: the definition proposed by the plan is the

¹⁷⁶ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

¹⁷⁷ <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

¹⁷⁸ <http://lesdonnees.e-cancer.fr/>

¹⁷⁹ <http://www.e-cancer.fr/toutes-les-actualites/360/6714-synthese-de-lactivite-2010-des-centres-experts-cliniques-pour-cancers-rares-de-ladulte>

¹⁸⁰ http://www.e-cancer.fr/component/docman/doc_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares

¹⁸¹ http://www.e-cancer.fr/component/docman/doc_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts

¹⁸² http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

¹⁸³ <http://www.e-cancer.fr/toutes-les-actualites/360-les-soins/7283-genetique-moleculaire-des-cancers-deux-nouveaux-rapports-sur-la-prise-en-charge-personnalisee-des-patients#>

¹⁸⁴ Called “Schéma national handicaps rares” (“National Scheme for Rare Disabilities”): http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

¹⁸⁵ One of the measures of the plan was to compare this notion with other concepts used in France or in other countries. The INSERM (French National Institute for Healthcare and Medical Research) set up an expert working group in charge of analysing this notion. The

coexistence of a prevalence of no more than 1 in 10 000 people, a rare combination of severe deficiencies or diseases (vision or hearing disability, dysphasia, severe epilepsy etc.), complex care and rarity of competent professionals. The main objectives of the plan are:

- The centralisation and dissemination of information on rare disabilities in collaboration with Orphanet;
- The consolidation, development and evaluation of specialised expertise at national level;
- The reinforcement and organisation of the identification of rare disabilities and multidisciplinary functional evaluation across France;
- The creation of inter-regional relays;
- The development of the offer of services at home and in establishments for patients with rare disabilities.

Several levels of expertise for patients with rare disabilities are planned. Three national “resource centres” were created in 2011 for patients with a visual or hearing deficiency associated with other deficiencies or diseases. A fourth national “resource centre” for patients with rare disabilities and severe epilepsy was created in 2012. Inter-regional relays of these national centres will be created during 2013. Cooperation between national “resource centres” and inter-regional teams for rare disabilities and “reference centres” for rare diseases is also planned.

Other French national initiatives related to rare diseases

On 16 May 2008, the French Ministry of Health announced the second National Plan for Autism for the period 2008-2010. This plan aimed at improving the diagnosis and the treatment of patients with autism, children and adults, their access to social and educational services, and the information of health professionals. In 2011, the evaluation of this plan began in the perspective of a next third plan¹⁸⁶.

In June 2008, a national plan concerning visual handicap (of which rare diseases may be a cause) for the period 2008-2011 was published. This plan aimed at improving treatment, social care, mobility and social integration of people with visual handicap¹⁸⁷.

In February 2010, a national plan concerning deafness and hearing-impairment (of which rare diseases may be a cause) for the period 2010-2012 was published¹⁸⁸, with 52 measures including: improvement of the prevention and screening of hearing disorders; better support of deaf and hearing-impaired people through their life; and enhanced access to social life.

The “*dossier medical personnel*” (“personal medical record” - DMP) is a national healthcare tool for sharing and exchanging information about individual patients. The DMP has been developed by the French Shared Healthcare Information Systems Agency (“*Agence des systèmes d’information partagés de santé*” - ASIP Santé) for the Ministry of Health. It is a secure electronic health record accessible on the Internet with full patient control of what it contains and what physicians may access. The aim is to provide physicians with a holistic picture of patients with complex conditions such as chronic diseases, and among them, rare diseases. It is thus expected to support the coordination of the different specialists, GPs and centers of expertise involved in the follow-up of patients and improve the quality of care. Two years after the DMP was launched, there were 250 000 DMP at the end of 2012.

The French National Authority for Health (“*Haute Autorité de santé*” – HAS) and the French Biomedicine Agency (“*Agence de la biomedicine*”) signed a collaboration on 14 December 2010¹⁸⁹ to work together during 3 years on a project to improve healthcare in four fields in which the Agency is principally involved: organ donation, transplants, medically assisted reproduction and human genetics. The French Biomedicine Agency follows the different tests performed by French laboratories and publishes an annual report. This report communicates only diagnostic activities related to routine patient’s results excluding research genetic testing. It provides critical information to support rare diseases plan decision process at national level and gives a complete overview of genetic labs practice and technological evolutions and, to some extent, encourages genetic labs networking.¹⁹⁰

expertise report has been published in may 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>

¹⁸⁶ The third plan has been launched on may 2013: <http://www.social-sante.gouv.fr/actualite-presse,42/breves,2325/presentation-du-3eme-plan-autisme,15797.html>

¹⁸⁷ http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUN08.pdf; www.cnsa.fr/IMG/doc/Plan_handicap_visuel_1_-2.doc

¹⁸⁸ http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan_en_faveur_des_personnes_sourdes_ou_malentendantes_-_10_02_2010.pdf

¹⁸⁹ http://www.has-sante.fr/portail/jcms/c_1007980/la-haute-autorite-de-sante-et-lagence-de-la-biomedecine-sengagent-pour-ameliorer-la-qualite-des-soins

¹⁹⁰ www.agence-biomedecine.fr

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo (“Rare Diseases Cohorts”) project for a duration of 10 years and for a total of €10 million. The RaDiCo project finality is to create and follow selected cohorts of rare disease patients in the perspective of better annotating the phenotypes, better understanding the genotype-phenotype relationship, the natural history of rare diseases, and improving physiopathological, therapeutic or prognostic research. The RaDiCo program is dedicated to set up a platform pooling all the resources needed for rare disease cohorts in order to:

- Establish a common set of meaningful rare disease data/indicators collected from all the Reference and competence centres;
- Provide appropriate resources to clinicians/biologists expert in rare diseases;
- Be able to integrate rare disease data from different sources, requiring the development or improvement of the interoperability of different databases (data standardisation and harmonisation);
- Use common standards for data (including data description, data quality, interoperability, data exchange etc.);
- Ensure the long-term sustainability of these actions.

The RaDiCo project will take advantage of this platform to facilitate the emergence and the design of clinical and translational research programs on rare diseases in partnership with industry. Expected results of the above-mentioned actions are:

- Provision of methodological expertise to analyse rare disease data;
- Anticipation of future needs such as integration of data from systems biology and “omics” approaches.

The research programs resulting from this integrated view of rare diseases are:

- Economic and socio-economic aspects of rare diseases;
- Setting up a collection of induced pluripotent stem cells (iPS) for all rare diseases investigated in France.

In 2011, the web portal “Epidemiology – France”¹⁹¹ was launched, aiming to provide a directory of databases to advance research and expertise in the field of health in France. The “Epidemiology – France” portal was created under the auspices of the Strategic Council for the Health Industries (“Conseil stratégique des industries de santé” - CSIS), in collaboration between:

- AVIESAN (“Alliance nationale pour les sciences de la vie et de la santé” - French National Alliance for Life Sciences and Health);
- The French Ministry of Economy, Finances and Industry (General Directorate for Competitiveness, Industry and Services - DGCI);
- The LEEM (“Les entreprises du médicament” - French pharmaceutical industry association).

This portal aims to :

- Improve the availability of information;
- Locate existing skills and data by theme;
- Encourage transparency;
- Contribute to cooperation between research networks;
- Reinforce research quality;
- Foster the generation of new research projects;
- Promote partnerships and collaboration and increase value of health data.

It brings together information on approximately 493 databases and includes a search by the theme “Rare Diseases”; 25 databases classified in “Rare Diseases” are included in this portal with theme including mostly nationally designated registries.

Centres of expertise

The first National Plan for Rare Diseases (2005-2008) launched a structured organisation of healthcare for rare disease patients. A designation process was created to name centres of scientific and clinical expertise in the field of rare diseases. Four waves of designation took place between 2004 and 2007. By the end of the plan, 131 reference centres were named in university hospitals by the French Ministry of Health and received a specific funding for their missions. These designated centres have 6 main missions:

- To facilitate diagnosis and define the course of treatment. Each centre has a double role: it is an expert centre for one or several diseases for which it is designated, and it is a resource centre for patients referred to it.

¹⁹¹ <http://epidemiologie-france.fr/>

- To define, publish and update national clinical practice guidelines for rare diseases ("PNDS") in collaboration with the French National Authority for Health (HAS);
- To coordinate research and participate in epidemiological surveillance in collaboration with the French Institute for Public Health Surveillance ("*Institut de veille sanitaire*" – InVS);
- To participate in training and information programmes for health professionals, patients and their families, in collaboration with the French national Institute for Prevention and Health Education ("*Institut national de prévention et d'éducation pour la santé*" – Inpes);
- To coordinate networks of health professionals and social workers;
- To be the contact point for patient organisations and social workers.

Up to the end of 2012, the Reference Centres were evaluated over time, first through self-evaluation after 3 years as a designated centre, then through an external evaluation after 5 years. The external evaluation was organised by the HAS which published its 2010 activity report in 2011, with one section dedicated to its activity in the evaluation of Reference Centres¹⁹². During the first plan, a National Consultative Designation Committee ("*Comité national consultative de labellisation*") analysed the results of the external evaluation and gave advice to the Ministry of Health. This Committee has not been continued. The second national plan has planned a revision of the evaluation process, for which a "permanent working group" was created in 2011. The new process has been in progress in 2012 and will be definitively specified at the beginning of 2013. The evaluation process will be modified: each reference centre will establish an activity report each year and undergo an evaluation at 5 years according to modalities still under discussion. When the new process will be published, the missions of the "permanent working group" will evolve towards the analysis and the follow-up of the annual activity and 5-year evaluation reports of the reference centres. This working group will also monitor the development of the future national clinical networks.

A second type of expert centres was designated in 2008, named "*centres de compétences*". These regional centres were proposed by each reference centre and designated by French Regional Hospital Agencies ("*Agences Régionales d'Hospitalisation*" – ARH). The aim of these regional centres is to assume responsibility for diagnosis, treatment and follow-up of the patient close to their home, and to participate in the activities of the reference centres they are linked to. The regional centres have not received dedicated funding for their rare disease activities. They have not been included in the evaluation process of the reference centres, and will still stay out of the future evaluation process in progress. Currently 500 regional centres have been named corresponding approximately to 1 expert centre per region for each of the 18 groups of rare diseases identified in Orphanet reports. The regional centres will be included into the future national clinical networks in association with the Reference Centres they are linked to.

In June 2012, the French General Directorate for Provision of Healthcare launched a position paper¹⁹³ detailing the conditions for the establishment and renewal of "expert centres" so as to best respond to requests for designation of such centres. This position paper is not specific to rare diseases centres.

Rare cancers have been excluded from the first national plan for rare diseases (2005-2008) since a national plan for cancer including measures for rare cancers was already in place. The French National Cancer Institute (INCa) published a report^{194,195} on the organisation of healthcare for rare adult cancers. This organisation was one of the key actions of the Second National Cancer Plan for the period 2009 -2013: this includes the creation of a system of national "Expert Centres" and a network of regional centres for rare adult cancers. Since 2009, 23 national "Expert Centres" for 23 groups of rare adult cancers and four anatomical pathology networks - in charge of the double reading of sarcoma, rare malignant neuroendocrine tumours, malignant mesothelioma and lymphoma - have been set up and financed. Among their missions, these Expert Centres have to ensure diagnostic certainty by implementing a systematic second reading of the biopsy specimens, to assure a multidisciplinary expert discussion of the patient file for the choice of initial and subsequent treatments, and to facilitate the enrolment of patients in appropriate clinical trials.

Three "resource centres" for rare disabilities have been designated in 2011, and a fourth one at the end of 2012, in the Framework of the French National Plan for Rare Disabilities 2009-2013.

In 2011 the university hospitals of Angers and Nantes, in association, with the French Alliance for Rare Diseases ("*Alliance Maladies rares*"), created a platform to support rare disease patients in the Pays de la Loire Region. This unique platform (called "*Plateforme régionale d'information et d'orientation sur les maladies rares*" – PRIOR – Regional platform for information and guidance concerning rare diseases) consists of a team

¹⁹² http://www.has-sante.fr/portail/jcms/c_1070314/rapport-annuel-d-activite-2010

¹⁹³ http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir_35428.pdf

¹⁹⁴ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

¹⁹⁵ http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012

including neurologists, a dermatologist, a psychologist, an occupational therapist, a social worker and a coordination assistant. It aims to help patients to find their way in the health and social care system. In Montpellier and the Languedoc-Roussillon Region, a network was created by the Reference Centre in association with the French Alliance for Rare Diseases to provide support to patients with developmental disorders and training sessions for professionals of health and social sector.

In 2012, the Assistance Publique - Hôpitaux de Paris, the consortium of university hospitals of Paris, organised several meetings to set up closer links and common procedures between Paris Reference Centres and community social services which assess needs and meet requirements of rare disease patients with disabilities.

Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - "Improve knowledge of epidemiology of rare diseases" - of the first National Plan for Rare Diseases. The Committee aims at:

- Proposing a policy for registries based on healthcare and epidemiological research needs;
- Giving an opinion on whether to create new registries or maintain existing registries, and on the management of registries;
- Evaluating the quality of registries submitted to the Committee after a call for proposals each year: only registries recognised as good quality registries (from then on called "qualified registries") may receive a national public funding from Inserm, InVS or INCa);
- Helping to diffuse and valorise information produced by qualified registries.

Members of the Committee include official members (representatives of French Institute For Public Health Surveillance, French National Institute of Health and Medical Research, Ministry of Health, Ministry of Research etc.), professionals with expertise in the field of rare diseases, registries or public health, as well as two representatives of patients' organisations. They are nominated for a 3-year term, with renewable mandate. Until now, the evaluation of the quality of registries has been the only activity of the Committee. In 2008, 6 national registries were qualified by the Committee for the period 2009-2011, and three new national registries in 2010 for the period 2011-2013. In 2011, seven national registries already qualified obtained a new qualification for the period 2012-2015, and one registry were qualified for the period 2012-2014. In 2012, one register was qualified for 3 years (2013-2015). At the end of 2012, 12 national registries were qualified: thalassemia, Gaucher disease, histiocytosis, congenital neutropenia, Pompe disease, cystic fibrosis, biliary atresia, esophageal atresia, arterial pulmonary hypertension, hereditary immune system disorders, SDH-dependant hereditary paraganglioma, and inherited deficiencies of coagulation. In 2012, a reflection has begun on the questions of a possible evolution of the Committee's missions and the needs of the other registries and databases existing in France for support and evaluation.

The Second National Plan for Rare Diseases also foresees the creation of a National Rare Disease Database (BNDMR). Its primary objective is to describe the demand of care for rare diseases at a national level, as well as the offer of care, and to assess whether the offer matches the demand. A secondary objective is to help recruiting patients for clinical trials or rare diseases cohorts (RaDiCo project). The reference and regional centres for rare diseases will be the primary data providers as well as diagnostic laboratories (genetic, cytogenetic, etc.) or existing rare disease registries if appropriate. To achieve these objectives, the first step is to build a minimum data set (MDS): this MDS will be common to all rare disease reference centres and to all rare diseases. In 2012, a working group helped to build the MDS, which will be discussed and validated by the Steering Committee of the Plan at the beginning of 2013. The MDS will be entered through an application called BaMaRa ("Banque Maladies Rares"), either directly by the reference centres, or through their own application if appropriate. It will help gathering data at the reference centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act.

The French Institute for Public Health Surveillance (*InVS*) has already analysed some data collected via a range of available sources (The National Database of Medical Mortalities - CépiDC, The National Database of Inpatient Registrations - PMSI etc.) in order to build epidemiological indicators for a few rare diseases. This work has been cited in the Second National Plan for Rare Diseases and the first results are available online¹⁹⁶.

France contributes to several European rare disease registries including EUROCAT, EUROWABB, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EIMD, EUROWABB,

¹⁹⁶ <http://www.invs.sante.fr/surveillance/index.htm> (Section "Maladies Rares")

EUROTRAPS, CHS, EURO CARE CF, ECFS, INFEVERS, EDMUS, EHN-EUROHISTIONET, ESCROT-HU, SCLS registry, VALID and TREAT-NMD. In the domain of rare cancers, France contributes to European clinicobiological databases, as CONTICABASE (soft tissue and visceral sarcoma), CONTICAGIST (gastrointestinal sarcoma tumours), ENS@T-ACC (adrenal cortical carcinoma) and ENS@T-pheo (pheochromocytoma).

Neonatal screening policy

A neonatal screening programme exists in France for all newborns for the following four diseases: cystic fibrosis, phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, as well as for sickle cell anaemia only for newborns at risk of developing the disease.

In 2010, an assessment of the opportunity to extend neonatal screening to one or more inborn metabolic errors of metabolism by tandem mass spectrometry in the general French population began. The first results were published in 2011 by the French National Authority for Health (HAS). The HAS has recommended the extension of the neonatal screening programme to medium chain acyl-CoA dehydrogenase deficiency¹⁹⁷. The decision to put this recommendation into practice has not yet been taken. That requires reorganising first the neonatal screening programme because tandem mass spectrometry cannot replace all the existing screening techniques, and cannot be used in all the laboratories currently participating in the programme. Furthermore the HAS is still working on the possibility of extending the programme to other inborn metabolic errors and on the generalisation of sickle cell anaemia screening to all newborns in France.

Neonatal screening programme for deafness (of which rare diseases may be a cause), on which the HAS had given recommendations in 2007, was approved in April 2012. Screening for deafness was already performed in 51% of the French maternity hospitals using different methods. National specifications on screening methods will be published in 2013.

Genetic testing

The French Biomedicine Agency (*“Agence de la Biomédecine”*), a public organisation operating under the supervision of the Ministry of Health, was created under the Bioethics Law of August 2004. Its overriding function is to *“guarantee equity, ethics, and transparency for the activities under its responsibility and for anticipated developments”*. The Biomedicine Agency published its 2011 annual report¹⁹⁸ in 2012. For the third consecutive year, the Agency included data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The annual report revealed that 387 059 tests were performed in France in 2011. In the domain of molecular genetics (including pharmacogenomics), diagnostic tests were undertaken for 1 012 diseases of a total offer of 1 282 diseases for which testing is possible in France. Of these 1 282 diseases, 726 tests are available in only one French laboratory. As in previous years, two non-rare disease indications (haemochromatosis and non-rare thrombophilia) represented over 40% of the total analyses conducted in 2011.

In the arena of prenatal diagnosis (PND), of the 42 082 cases examined in 2010, 7 141 certificates were issued for a medical termination of pregnancy (MTP). Of these, 668 pregnancies were pursued although a MTP had been issued. Among MTP cases, 44% were performed for malformations or malformation syndromes, 38.5% for chromosomal abnormalities, 6.2% for genetic abnormalities, 2.7% for maternal conditions, and 0.8% for involved infections. Ultrasound is the most performed prenatal examination tool in France. Unregulated by law, its practice does not fall within the competence of the Biomedicine Agency. Biologically, PND involves sampling either the foetus and/or its annexes (amniotic fluid, chorionic villi, foetal blood), or the mother's blood. Among the 74 629 foetuses studied by cytogenetic analysis, 3 849 were affected. Among 2 728 foetuses studied by molecular genetics, 534 anomalies were detected. Biochemistry and foetal serum markers resulted in 27 diagnoses of hereditary diseases: 50 in endocrinology (abnormal genital or genotype-phenotype discordance, abnormal thyroid or 21-hydroxylase deficiency); 251 involved neural tube defects and 550 detected trisomy 21 (determined by serum markers on 660 629 women tested). The only non-invasive prenatal genetic diagnosis involves the analysis of foetal DNA circulating in the maternal blood, which yielded 5 921 diagnoses in 2009. The number of foetal Rh determination using this technique is increasing: from 384 cases in 2005 to 5 359 in 2009. Finally, assisted procreation procedures employing pre-implantation genetic diagnosis in 2009 led to the birth of 59 children in France (versus 71 in 2008).

The French Bioethics Law of August 2004 stipulated the prohibition of embryonic research, but allowed the possibility of research under certain conditions for a maximum of five years following the

¹⁹⁷ http://www.has-sante.fr/portail/jcms/c_1069254/evaluation-de-lextension-du-depistage-neonatal-a-une-ou-plusieurs-erreurs-innees-du-metabolisme-par-spectrometrie-de-masse-en-tandem-1er-volet-deficit-en-mcad

¹⁹⁸ http://www.agence-biomedecine.fr/IMG/pdf/ra_biomed_2011_bd_web.pdf

publication of the decree. The moratorium period expired in February 2011. Between September 2004 and February 2011, 173 permits to conduct such research were issued, of which 71 were for research protocols, 24 involved the conservation of embryonic stem cells and 46 the importation of embryonic stem cell lines. The revised Bioethics Law of July 2011 maintains the possibility of French scientists to conduct research under certain conditions. The Biomedicine Agency did not issue any new authorisations in 2011 after the end of the moratorium.

In 2006 a programme supporting the structuring of molecular genetics, including the development of 28 hospital-based platforms, was established in France. Amongst the services these platforms perform is molecular testing to identify genetic mutations in tumours, the identification of biomarkers for potential targeted therapies, diagnosis refinement, and prognosis establishment. The INCa reports show that the platforms' turnover is robust and growing, especially in the areas of haematology and solid tumours. Some 144 000 patients underwent molecular testing in 2010, versus 102 000 in 2009. The platforms have a catalogue of 60 tests available, as well as 14 determinants for access to targeted therapies already established or under development. Few new molecular tests were added in 2010, with the exception of IDH1 and IDH2 mutations in gliomas. Thus, the increased activity involves molecular tests already available in 2009. The second report¹⁹⁹ on molecular genetic testing for targeted multidisciplinary treatment, summarises the 2011 activities supported by INCa to bring targeted therapies to more patients. In 2010, 61 000 patients underwent testing and were offered a tailored treatment strategy, up from 42 874 patients in 2009 and 31 965 in 2008. Both of the new INCa documents report on activities stemming from specific measures of France's Cancer Plan (2009-2013) that seek to ensure equal access to treatment, and develop molecular genetics platforms for hereditary cancers.

The final text of the Bioethics Law²⁰⁰ was adopted on 23 June 2011 and published in July 2011. The text includes indications on how to inform family members in the case of genetic disease, as well as the delivery of tests proposed to pregnant women. The legislation on research using embryos will remain unchanged.

National alliances of patient organisations and patient representation

The *Alliance Maladies Rares* (French Alliance for Rare Diseases) is the national umbrella organisation dealing with rare diseases. It plays a major role in organising working groups, communicating on rare diseases, offering support to organisations of patients and families, and contributing to the development of the French National Plans for Rare Diseases and their evaluation. The Alliance played a major role in the elaboration of the first and second National Plan and in the evaluation of the Reference Centres. The Alliance celebrated its 10 anniversary in 2010 and marked the occasion with a meeting of its members on 15 February 2010 in Paris: the Alliance's new website was launched as were the forthcoming information documents created by the Alliance. In 2011 the Alliance launched a practical guide and made it available for its members and in centres of expertise for rare diseases. The guide is intended to patients and their families, and provides information on the organisation and availability of expert care and the services. The guide also gives information on the rare disease patients' organisations in France. The Alliance also launched an awareness raising campaign aimed at children via the newspaper for children called *Le Petit Quotidien*; information packs for teachers were also made available to help classes understand what is a rare disease and life for children with such a condition.

The *Alliance Maladies Rares* and other patients' organisations have received some public funding during the first and second National Plans for their various support activities and awareness campaigns.

Seventeen patients' organisations in the field of rare cancers collaborate daily with the existing rare cancer national expert centres. Several have been involved as soon as the designation of these centres. They play a major role in diffusing high quality information both on the healthcare services available and on access to innovative treatments.

Sources of information on rare diseases and national help lines

Orphanet activities in France

Concerning actions to improve public information, financial support for the French Rare Disease Platform ("*Plateforme Maladies Rares*", established in 2001 in Paris), and more particularly for the Orphanet web portal, has been reinforced under the two National Plans. The French Ministry of Health has supported strongly the launch of the Orphanet Joint Action financed by the European Commission.

¹⁹⁹ http://www.e-cancer.fr/component/docman/doc_download/8310-molecular-genetic-testing-for-equal-access-to-targeted-therapies-in-france-in-2011

²⁰⁰ <http://www.service-public.fr/actualites/001820.html>;
<http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024323102&dateTexte=&oldAction=rechJO&categorieLien=id>

Orphanet was established in 1997 and is the reference for all rare disease information in France. The team, hosted by the French National Institute of Health and Medical Research (Inserm) in Paris, is in charge of collecting data on services for rare diseases (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patients' organisations) in France, and of coordinating the activity of Orphanet's external teams across Europe, as well as maintaining the encyclopaedia and inventory of rare diseases. The team also maintains the Orphanet France²⁰¹ national website. Recent new Orphanet features include the encyclopaedia for patients in French, emergency guidelines, a search by sign facility and a national entry point for France in French. Since 2003, Orphanet also edits a twice-monthly newsletter concerning political and scientific news in the field of rare diseases and orphan medicinal products entitled *OrphaNews France*.

In December 2009, Orphanet signed a partnership with the National Solidarity Fund for Autonomy (CNSA) and leads a project, in the framework of both the National Plan for Rare Disabilities and the National Plan for Rare Diseases, to develop and make available the information concerning the disabilities caused by rare diseases. Orphanet will introduce specific chapters on disability in the General Public encyclopedia concerning rare diseases responsible for disability. In addition to this, the disabilities associated with rare diseases will be indexed with the WHO's ICF (International Classification of Functioning, Disability and Health), in order to allow rare diseases to be found when searched by any kind of disability. The first 3-year cooperation has been an opportunity to develop information on some crucial aspects of rare diseases that have not yet been specifically addressed before in Orphanet. This information will be useful to patients, families and professionals dealing with disabilities. The CNSA decided to maintain the cooperation for three more years in March 2013.

The INCa signed an agreement with Orphanet to share information on organisation for rare cancers. Recently, Orphanet published a document describing the clinical networks (national and regional expert centres) for rare cancers²⁰².

Official information centre for rare diseases

Orphanet is the official source of information on rare diseases in France.

Information on rare cancers organisation is available on the INCa website²⁰³. Ten national expert centres have elaborated dedicated websites with high quality information available for the patients.

Help line

The help line *Maladies Rares Info Services* provides support and information on rare diseases. It is the first health information service in France to have a quality certification (ISO 9001). This service launched in 2011 and has continued in 2012 to propose a series of Internet chat sessions on the first Monday of each month: each session has a theme and Internet users can ask the team questions during the hour-long sessions. *Maladies Rares Info Services* also implemented a "rare diseases barometer". The purpose of this barometer is to collect objective data on the issues to which patients are confronted. Data were collected by means of qualitative and quantitative surveys targeting users of the information and support service. The results of the first round of these surveys were published in 2012²⁰⁴. The service also launched a forum for its users in 2012.

The AFM (*Association française contre les myopathies*, French Muscular Dystrophy Association) provides a help line for information on neuromuscular diseases.

Other sources of information on rare diseases

The French National Agency for the Safety of Medicine and Health Products ("*Agence Nationale de Sécurité du Médicament et des Produits de Santé*" – ANSM, ex-AFSSAP²⁰⁵) has published on its website since 2009 a registry of clinical trials on medicinal products conducted in France including those on rare diseases, an updated list of compassionate use authorisations (cohorts) with respective summary of product characteristics and leaflet, updated list of medicinal products available within nominative temporary use authorisations (ATU) with specific information if applicable and other general information on hospital preparations.

During the first National Plan for Rare Diseases, the French General Directorate for Health ("*Direction Générale de la Santé*" - DGS) in the Ministry of Health has produced some information cards to be used in case

²⁰¹ <http://www.orphanet-france.fr/national/FR-FR/index/page-d-accueil/?lng=FR>

²⁰² http://www.e-cancer.fr/component/docman/doc_download/9123-cahiers-dorphanet-centres-experts-cancers-rares

²⁰³ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

²⁰⁴ <http://www.maladiesraresinfo.org/news/observatoire-maladie-rare-maladies-rares.html>

²⁰⁵ The AFSSAPS was given a new name and new missions on 1 May 2012, following the French law reinforcing the monitoring of safety of medicinal and other health products, published on 29th December 2011: *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (French National Agency for Medicine and Health Products) <http://www.ansm.sante.fr/>.

of emergency by rare disease patients. These cards were developed in close collaboration with health professionals, Reference Centres and patient organisations. Each card had two parts: a first one with information about the patient's health status intended for healthcare professionals, and a second one with brief general information on his/her disease for the patient and for non-specialist healthcare professionals²⁰⁶. These cards were distributed by the Reference Centre physicians. During the second plan, a simpler model will be developed, just specifying some information on the patient and on his/her disease (name of the disease, Orpha number, Reference Centre, what to do and not to do in case of emergency) to be used in case of emergency.

In 2010, the site www.droitsdesmalades.fr, which informs all citizens about their healthcare rights, was launched. In addition, the patient organisation *Sparadrap*²⁰⁷ has published an informative guide concerning children's rights when they are admitted into healthcare facilities, including issues such as consent to participate in research and financial aid.

The website *Intégrascal* gives information on chronic diseases, in particular rare diseases, for teachers and education professionals in charge of pupils with chronic disease or disabilities. This website free of access contains brief medical and educational information useful for education professionals to adapt teaching to the children with the aim of better integration into school²⁰⁸.

Good practice guidelines

Since the beginning of the first national plan, the Reference Centres produced, with the help of the HAS, 49 national good practice guidelines ("PNDS") for diagnosis, treatment and follow-up of patients with rare disease. These guidelines are published on Orphanet, HAS²⁰⁹ and Reference Centre websites. The HAS itself has published clinical practice guidelines²¹⁰ for the follow-up of children with deafness under the age of six and their family. At the end of 2012, the HAS published a new simplified method to develop "PNDS"²¹¹ to help the Reference Centres draft more quickly the PNDS.

Concerning rare tumours, two national good practice clinical guidelines were published with the quality label of HAS and INCa respectively in 2010, the first one concerning surgical practices in digestive neoplasia, including peritoneal pseudomyxoma, and the second one gestational trophoblastic disease²¹². Clinical guidelines are available on the dedicated websites of national expert centres, concerning cutaneous lymphoma, rare head and neck cancers, thyroid carcinoma, rare ovarian carcinoma, thymus carcinoma.

Training and education initiatives

All health professionals, medical doctors, midwives, nurses and paramedics follow two hours of training during their undergraduate medical studies on the topic of rare diseases. Every year, 3rd year medical students at the Necker-Cochin faculty of medicine in Paris are offered an optional 30-hour training course on rare diseases during which experts in the field and representatives of rare disease patient organisations are present.

The Paris-based Institute of Myology organises an annual Summer School in Paris: this offers the possibility to train in myology via a condensed 10-day course.

National rare disease events 2012

Each year in December, an annual *Téléthon* is organised by the AFM (*Association française contre les myopathies*) over 30 hours to raise funds. The funds raised go towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. In 2012, the 26th edition of the *Téléthon* took place on 8-9 December, raising 81 million Euros. On 8 December 2012: the AFM launched a new English language website to present the aims of the organisation and the projects the AFM is funding. Each year, to coincide with the *Téléthon*, the *Alliance Maladies Rares*, in association with the AFM and the *Fondation Groupama pour la santé* (Groupama – one of the major French mutual insurance companies – Foundation for Health), organises a Rare Disease March (*Marches des Maladies Rares*) involving patients and patients' organisations. In 2012, the annual Rare Disease

²⁰⁶ <http://www.sante.gouv.fr/les-cartes-de-soins-et-d-informations-pour-les-personnes-atteintes-de-maladies-rares.html>

²⁰⁷ <http://www.sparadrap.org/SPARADRAP>

²⁰⁸ <http://www.integrascal.fr/>

²⁰⁹ http://www.has-sante.fr/portail/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=1

²¹⁰ http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf

²¹¹ http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=2

²¹² http://www.has-sante.fr/portail/jcms/c_1147273/fr/tableau-des-recommandations-de-bonne-pratique-ayant-obtenu-le-label-methodologique-inca-has?xtmc=&xtcr=2

March gathered around 2 000 people in Paris. The *Téléthon*²¹³ and Rare Disease March²¹⁴ aim to raise awareness about rare diseases in addition to the Rare Disease Day which is celebrated each February.

On 29 February 2012, on the occasion of the Rare Disease Day, the *Fondation maladies rares* (Rare Diseases Foundation) was officially launched at the French Academy of Sciences with a dedicated evening event which gathered 150 participants and welcomed speeches from its founding members. A press release also acknowledged the creation of the Foundation, a unique alliance of actors from research, care and patients' organisations devoted to speeding up and stimulating research in rare diseases. In addition to this, the *Alliance Maladies Rares* and Orphanet organised an awareness-raising day with the French railway company SNCF: they were present on a number of high speed trains leaving Paris for other major towns. On the same day in Paris, members of the Rare Diseases Platform came together in front of the Eiffel Tower to raise their hands in support of patients for the Rare Disease Day. A range of activities were organised in towns across France by patients' organisations to raise awareness of the Day and rare diseases in general.

In September 2012, Orphanet held its 13th Forum for Patient Organisations in Paris, in collaboration with the *Alliance Maladies Rares*. The sessions centred on clinical and emergency online guidelines for rare diseases developed by Orphanet and on personal electronic medical records in the French healthcare system, as well as advances in the area of research, and the recent launch of the French Rare Disease Foundation.

Hosted events in 2012

Amongst the events hosted by France in the field of rare diseases were: EUCERD/Eurogentest workshop on coding rare diseases and describing phenotypes (27 -28 September 2012, Paris), International Symposium on Hepatic Glycogen Storage Diseases (4-6 April 2012, Lyon), Sixth International Alkaline Phosphatases Symposium (16-19 May 2012, Huningue), European Working Group on Gaucher Disease Meeting (28-30 June 2012, Paris), World Federation of Hemophilia World Congress (8-12 July 2012, Paris), Mechanisms of Intellectual Disability: From Genes to Treatment (3-7 October 2012, Roscoff), 7th World Rett Syndrome Congress (22-26 June 2012, Paris, France), OroDysmorphology course (24 May 2012, Strasbourg), ESH-ENERCA Training Course: Diagnosis and Management of Very Rare Anaemias (3-4 February 2012, Paris). The IRDiRC held its Executive Committee Meeting on 25-26 September 2013 in Evry, and the Interdisciplinary Group held a meeting on 9-10 November 2012 in Paris.

Research activities and E-Rare partnership

National research activities

In France, public funding is available for rare disease research projects from:

- The National Agency for Research (*Agence Nationale de la Recherche* – ANR) for basic research;
- The General Directorate for Provision of Healthcare (*Direction Générale de l'Offre de Soins* – DGOS) of the Ministry of Health for clinical research via funding of the "PHRC" ("*Programme Hospitalier de Recherche Clinique*" – Hospital Clinical Research Programme) sponsored by National Health Insurance of the French Social Security System;
- The INSERM for translational research;

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which will be launched at the beginning of 2013 ("*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health²¹⁵). This call for proposals is not specific for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

In addition, some charities, private foundations or patient organisations provide funding for research, such as the AFM.

The "*Fondation maladies rares*²¹⁶" (*Rare Diseases Foundation*) was approved by a decree of the French Ministry of Research and Higher Education on 6 February 2012, and officially launched on 29 February 2012. The creation of this rare diseases research foundation is a measure delineated in the research objectives of the second French Plan for Rare Diseases 2011-2014. The Foundation is a private, non-profit structure endorsed by both the French Ministry of Research and the French Ministry of Health to coordinate, federate and fund rare diseases research. Its main aim is to accelerate and promote technological, medical and social innovations to the benefit of the rare disease patients. The Foundation gathers French rare disease research into one

²¹³ <http://www.afm-telethon.fr/le-telethon/le-telethon-2011>

²¹⁴ <http://www.alliance-maladies-rares.org/article/marche-des-maladies-rares-2011-98>

²¹⁵ <http://www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/>

²¹⁶ <http://fondation-maladiesrares.org/>

cooperative structure that operates with a sustained source of funding to bring a new synergy to fundamental, clinical and translational research. Its funding bodies represent a unique alliance of research, care and patient organisations. The funding bodies are: the AFM (French Muscular Dystrophy Association), the French Alliance for Rare Diseases Alliance (*Alliance Maladies Rares*), the French National Institute of Health and Medical Research (Inserm), the Conference of General Directors of the University Hospitals and the Conference of University Presidents. The Foundation is administrated by an Executive Board, composed of representatives from each of the funding members and eight renowned experts in research and academia. Furthermore, the Foundation benefits from the guidance of a Scientific Committee composed of French and International leading medical specialists and scientists in the rare diseases field, encompassing both biomedical and social and human sciences fields. The Foundation is based in the “*Plateforme Maladies Rares*” in Paris. It consists of a team of twelve people, including seven Regional Delegates, who ensure the linking of actors as well as the development of rare diseases research programmes.

In 2012, several activities have been developed around 6 main objectives that structure the Foundation working programme:

1. Boosting research by facilitating access to technology platforms and launching calls for tenders;
2. Developing research in social and human sciences applied to the rare diseases field;
3. Supporting the setting up and development of preclinical and clinical trials;
4. Participating in and developing European and international rare diseases dedicated research programmes;
5. Being involved and proactive in the public health and research policies and frameworks;
6. Supporting and valorising rare diseases data collection according to state of the art national and international frameworks.

As far as calls for proposals are concerned (Point 1), the French Rare Diseases Foundation is offering funding opportunities both for biomedical research and social and human sciences. In the biomedical field, three different project calls were launched to increase access to High Throughput Sequencing in May 2012, September 2012 and February 2013 respectively. A total of 55 projects have been funded in 2012 with the aim to identify new genes responsible for rare diseases. The Foundation works in close collaboration with state of the art public and private technological platforms and is establishing partnerships to facilitate general access to resources for rare diseases research, also outside its own funded calls. New themes for calls for proposals, especially designed according to the needs identified from the extensive regional coverage of research teams, will be implemented on a regular basis. In addition to exome and genome sequencing calls for proposals, the Foundation also funds animal models through bi-annual calls for proposals (the first call will be launched on mice models in February 2013) as well as the screening of innovative molecules.

In addition to the calls for projects, an important milestone has been reached in 2012 with the online release of an extensive mapping of funding opportunities for rare disease research (including institutional funding, charities, private, and EU and international funding). This unique and regularly updated portal, established by the Foundation in collaboration with the ANR and the DGOS, gives a better visibility to researchers seeking funding. Of note, this provides, within a single platform, information to the French rare diseases community on funding opportunities available at the French regional and national levels as well as at the EU level (including for instance programmes such IMI, COST, FP7, DG SANCO). Information is relayed and extended locally by the Regional Delegates.

In December 2012, a first call for proposals was also launched in the field of human and social sciences (Point 2) jointly by the Foundation, the French National Solidarity Fund for Autonomy (CNSA) and the General Directorate for Health (DGS) to support human and social sciences research while encouraging cross-disciplinary studies by involving patients' organisations and clinicians together with dedicated academics. This call for proposals addressed three different areas: the diagnostic pathway; new technologies in the field of genetics and consequences for patients including ethical issues; and the social, educational and professional pathways for rare disease patients. More than 70 projects have been submitted to this first call for proposals underlying the need of additional calls to be launched on a regular basis.

The Foundation aims to boost clinical trials in rare diseases (Point 3) by identifying and supporting innovative medical devices as well as molecules with therapeutic benefit. Dedicated new public-private partnerships are under development. The objective is to provide guidelines, methodological support and search for partners in the development of preclinical and clinical studies linking academia and industry.

In order to promote French research, increase international collaborations and influence global related policies (Point 4), the Foundation has been actively involved in a number of international programme. In 2012, the Foundation, together with Orphanet, has been awarded the scientific organisational support of the International Rare Diseases Research Consortium (SUPPORT-IRDIRC, coordinated by Orphanet) and has joined

the integrated infrastructure programme RD-Connect as an official partner in order to assess the project's impact and the appropriateness of the implementation of shared databases with the needs of the international research community. The Foundation also supported the collaborative Mediterranean Myology School initiative of Saint-Joseph University, (Beirut, Lebanon, by funding three traveling grants, hence promoting expertise sharing in the Mediterranean area.

Beyond workshops jointly organised with French National Alliance for Life Sciences and Health (*Alliance nationale pour les sciences de la vie et de la santé - Aviesan*) on timely themes including proteomics and model organisms, the Foundation has initiated collective initiatives (Point 5), in 2012, on rare diseases issues, such as a think-tank of pharmaceutical companies and awareness actions together with the international business school ESSEC, that are to be continued in 2013.

Since its setup, the Foundation has been working closely with the representatives of the national data collection programme respectively initiated by the French Ministry of Health and the French Ministry of Higher Education and Research, namely the National Rare Disease Database (BNDMR) and the RaDiCo Project (Point 6).

In September 2012, the French Institute of Rare Disease Biotherapies was launched, grouping together the actions of Genethon, the French Muscular Institute, I-Stem and the Genetic Therapy Pole of Nantes under the coordination of the AFM, to cover all the stages of research. The Institute will bring together hundreds of experts and researchers.

In the scope of the Second French National Plan for Rare Diseases, €9.6 million were dedicated by DGOS in 2011-2012 to upgrade next generation sequencing platforms.

Other funding opportunities for rare diseases research in 2012 included grants and calls launched by the following organisations/institutes: Agence nationale de sécurité du médicament et des produits de santé (ANSM), International Fund for research on Congenital Adrenal Hyperplasia, Fondation Jérôme Lejeune, Fondation Thierry Latran, Fondation des Entreprises du Médicament, Fondation Imagine, Association Française de l'Atrésie de l'œsophage, Association Française de l'Ataxie de Friedreich, Association pour l'information et la recherche sur les maladies rénales génétiques (AIRG-France), Institut de Recherche en Santé Publique (IReSP), Association Française du Syndrome de Rett (AFSR), Fondation Motrice, and l'Agence de la biomedicine.

Organisation into expert centres for rare adult cancers contributes to promoting research on these rare cancers through multicentre research studies, either basic, translational or clinical, at national or international level. Therefore, in 2011, 46 new clinical trials were initiated or ongoing and 16 finalised, with a total of more than 800 patients with a rare cancer included in a clinical trial.

Participation in European projects

France participates, or has participated, in European rare disease research projects including: ARISE, ANTEPRION, ANTIMAL, ALPHAMAN, AUTOROME, BIOMALPAR, BALANCE, BIO-NMD, BRAINCAV, BNE, CARDIOGENET, CAV-4-MPS, CUREFXS, CELLPID, CLINIGENE, CONTICANET, CONTICABASE, CHEARTED, CRUMBS IN SIGHT, CUREHLH, CRANIRARE, DSDLife, DARTRIX, ELAST-AGE, EDEN, EPOKS, EMINA, ERMION, EVI-GENORET, EPINOSTICS, EUROBFNS, EuroGeBeta, ENRAH, ENCCA, ENS@T-ACC, EUROMICS, EUNEFRON, EMSA-SG, EUMITOCOMBAT, EURAMY, EUREGENE, EuRenOmics, EUROCARE-CF, EUROAGENTEST, EUROAGENTEST2, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROAS, EURO IRON1, EURO-LAMINOPATHIES, EURORETT, EURO-CDG, EURO-SCAR, EUROSCA, EURSPA, EUROTRAPS, EUROWABB, ENCE-PLAN, EUROSARC, ESPOIR, EUSTAR, EPOKS, EURO-PADNET, EURIOFNET, FAD, GETHERTHAL, GENESKIN, GENEGRAFT, GRIP, GENOMIT, GENOSTEM, HMA-IRON, HSCR, HEMO-IPS, HAEIII, HUE-MAN, IPF-AE, IMPACTT IMMOMEC, INNOVALIV, INHERITANCE, INTREALL, IMMUNOPRION, KINDLERNET, LEISHMED, LYMPHANGIOGENOMICS, MANASP, MILD-TB, MITOCIRCLE, MM-TB, MTMPATHIES, MTMPATHIES2, MPCM, MITOTARGET, MYASTAID, MYORES, MYELINET, NEUROBID, NEOTIM, NEUPROCF, NMD-CHIP, NOVSEC-TB, NM4TB, NEUROSIS, NEUROPRION, NEUROMICS, NOVELPID, NEMMYOP, NEUTRONET, NSEuroNet, OCTIPS, OVERMYR, OSTEOPETR, PODONET, PEMPHIGUS, RARE-G, RATSTREAM, RAPOSDI, RD-CONNECT, RISCA, SKIN-DEV, STRONG, SKINTHERAPY, STEM-HD, SIOPEN-R-NET, RHORCOD, RDPLATFORM, SUPPORT-IRDiRC, TB CHINA, TRANSPOSMART, THERAPEUSKIN, TUB-GENCODEV, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPath.

E-Rare

The *GIS Maladies Rares* was the coordinating partner of the E-Rare for Research Programmes on Rare Diseases, and organised the first joint transnational call in 2007²¹⁷ for research on rare diseases, with the participation of 6 countries and a total of 13 funded consortia (French research teams participated in each of these funded

²¹⁷ http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf

projects/consortia). France took part in the 2nd E-Rare Joint Transnational Call in 2009 and is represented in 11 of the 16 consortia selected for funding, with funding totalling around €2 million. France also took part in the 3rd transnational call launched at the start of 2011 in the context of E-Rare2: French research teams have been funded to participate in 13 of the projects selected for funding. France participated in the 4th Joint Transnational Call in 2012, with French teams participating in 7 out of the 11 consortia selected for funding. Starting April 2013, the Rare Diseases Foundation will be in charge of E-Rare 2 coordination on behalf of Inserm.

IRDIRC

The AFM (French Muscular Dystrophy Association) and French National Agency for Research (*Agence Nationale de la Recherche*) are committed members of the International Rare Disease Research Consortium.

Orphan medicinal products^{218,219}

Four institutions are involved in the field of orphan medicinal products on the French market: the French National Agency for the Safety of Medicine and Health Products (ANSM, ex-AFSSAPS), the French National Authority for Health (HAS), the French Economic Committee for Health Products (*Comité Economique des Produits de Santé* – CEPS), and the Ministry of Health.

The LEEM (French Pharmaceutical Industry Association) is a constituted professional organisation that represents the pharmaceutical industry in France, i.e. the companies whose missions are research, development, manufacturing and marketing of medicinal products. Rare diseases became priority action in the LEEM's strategy in 2002: a rare disease working group made up of key stakeholders in the public and private sectors meets regularly to discuss: innovative therapies for rare diseases (and how to bring these therapies to patients), the provision of health care for rare disease patients, the communication of information on rare diseases and treatment, ways to create the correct conditions for optimal and innovative clinical treatment and ways to support the national plan for rare diseases. The LEEM organises a workshop dedicated to orphan medicinal products every year. Since 2001 the LEEM evaluates the advances made in clinical research in France, including clinical research in the field of rare diseases. The LEEM presented its annual overview of therapeutic advances with an edition covering 2012. A particular emphasis was put on new orphan drugs in relation to the development of personalised medicine²²⁰.

Orphan medicinal product committee

There is no orphan medicinal product committee currently in France, apart from the multistakeholder group at the LEEM (see above).

Orphan medicinal product incentives

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: *GIS Maladies Rares*, the Hospital Clinical Research Programme ("*PHRC*"). During orphan medicinal product development, free scientific advice is available from the ANSM; and budgetary incentives (from 2001) are available in the form of a tax exemption. Other incentives measures, such as free early advice and fast track process of the assessment for reimbursement by the Transparency Committee (CT) are performed by the HAS.

Free scientific advice is available for medicines from the ANSM as well as CT and compassionate use authorisation (cohort ATU) from the ANSM. The HAS is performing early meetings at the national level, the European level (within the EUNETHTA network of Health technology agencies) on request of pharmaceutical industry or on its own request. These scientific meetings aim to let the marketing authorisation (MA) owner know what data the HTA bodies expect especially concerning the relative effectiveness assessment in usual care.

Sponsors of orphan medicinal products are exempted from taxes to be paid by companies:

- Tax on the turnover of medicinal products if under €20 millions;
- Tax on the promotion of medicinal products, based on their promotion costs if turnover under €30 millions;
- Taxes paid in France by the companies on their sales (there is no turnover threshold for these taxes);

²¹⁸ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

²¹⁹ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

²²⁰ <http://www.leem.org/les-essentiels-maladies-rares>

- The safeguard clause for medicinal products whose turnover is under €30 millions;
- Tax on direct sales for medicine whose turnover is under 30€ millions;
- Tax on the distribution of medicines for medicine whose turn over is under 30 € millions.

These are some of the initiatives aimed at stimulating research by the pharmaceutical industry into rare diseases in addition to the provisions of the European Regulation on Orphan Medicinal Products.

The public authorities decided in 2010 to abrogate the framework agreements which exempt orphan medicinal products from certain regulations, and recommended price cap for orphan medicinal products costing more than €50 000 per year and per patient. An obligation to treat all affected patients was also proposed.

A law adopted by Parliament on 22 March 2011 will allow non-profit organisations to become pharmaceutical establishments and will give the status of medicine to gene-therapy products. As a direct result, the Généthon Bioprod non-profit laboratory, inaugurated in November 2010, will be able to produce products for gene-therapy for clinical trials.

Orphan medicinal product pricing policy

Before any pricing, all drugs including orphan medicinal products are assessed by the Transparency Committee of the HAS for reimbursement purpose. This committee provides the Ministry of Health and National Health Insurance with an opinion about the pertinence of reimbursement and the level of copayment, and specifies the added value of the drug, which is the basis for price definition. For innovative drugs (new therapeutic modality, presumably efficient and well tolerated, and covering an unmet medical need), often including orphan medicinal products, the Transparency Committee performs a fast track assessment before MA and delivers its opinion shortly after MA is granted. However, the official process starts after MA. This fast track reduces the usual timelines, which is of 90 days after MA, to 15 days.

After that step, an Industry-government agreement via the French Economic Committee for Health Products (CEPS) is defined, which sets the rules for the pricing of reimbursed medicines in France.

HAS also provides early dialogues for medicines that are under development in order to answer questions that the sponsor wants to ask about the way the development should go to *in fine* provide most adequate evidence of clinical interest for the patient and the public health. This is particularly adapted to orphan drugs that usually bring innovation for a limited population in a situation where the need is not covered.

Orphan medicinal product market availability situation

According to the registry of the French National Agency for the Safety of Medicine and Health Products (ANSM) website, the availability of orphan medicinal products in France can be represented as follows:

- Orphan medicinal products with valid market authorisation and with mention of commercialisation: Adcetris, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Ceplene, Cystadane, Dacogen, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyf, Firdapse, Flisint, Gliolan, Glivec, Increlex, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nexo-Brid, Nplate, Orfadin, Pedeia, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Signifor, Siklos, Soliris, Somavert, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Vyndaqel, Wilzin, Xagrid, Yondelis, Zavesca.
- Orphan medicinal products with valid market authorisation without mention of commercialisation: Bronchitol, Glybera, Mepact, Peyona, Plenadren, Revestive, Xaluprine.

Orphan medicinal product reimbursement policy

Orphan medicines can be dispensed in out-patient or in-patient settings through one of the two corresponding lists: list for medicines reimbursed by National Health Insurance and available in community pharmacies, and list for hospital pharmacies. Within the hospital list, the drugs are generally funded through *GHS* (*Groupes H*, a diagnostic-related group system established by the *T2A* ("*tarification à l'activité*", Hospital Activity-Based Payment) policy. However, some expensive drugs used in hospitals are fully reimbursed to the hospitals by the National Health Insurance. These drugs are listed in a specific list (called "*liste hors GHS*") established by the French Ministry of Health. Some of the drugs available in hospital pharmacies can be made available to outpatients (retrocession list) and paid for by the National Health Insurance. Within the 68 orphan medicinal products that have been granted MA in Europe, 3 have not requested reimbursement and within the 65 medicines remaining, all but two have been granted a positive advice for reimbursement in France.

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*²²¹, "particular prescribing conditions are in place for: drugs for hospital use, drugs with hospital prescription, drugs with initial hospital prescription, drugs with prescription only by specialists, drugs with a particular follow up during the treatment." From 1 January 2010, the Ministry of Health and the French National Health Insurance made it mandatory for the first prescription of an orphan medicinal product to be validated by a relevant Reference Centre when available, or by the regional centre directly linked to the relevant Reference Centre.

Other initiatives to improve access to orphan medicinal products

Compassionate use for individual patients takes the form of either cohort use (cohort Temporary Authorisation for Use) or named patient supply (nominative Temporary Authorisation for Use) prior MA granted both by the ANSM. Patients can also be treated with drugs before these drugs have received MA through clinical trials or hospital preparations. Reimbursement measures are in place for compassionate use. Innovative drugs are eligible for an ATU ("*Autorisation temporaire d'utilisation*" - Temporary Authorisation for Use) from the ANSM if there is a public health need.

This process was modified in 2012 following the law reinforcing the monitoring of safety of drugs and other healthcare products, published on 29 December 2011 (Law N° 2011-2012). The new law maintains the possibility of an ATU, in particular in the case of rare diseases. The drug must fulfil the following criteria: the treatment cannot be postponed; there is no alternative therapeutic to the drug; the efficacy and security of the drug are strongly presumed from the results of clinical trials (cohort ATU) or from scientific published data and knowledge (nominative ATU); the patient cannot be treated within a clinical trial. The ATU is given for a limited period, but renewable. A therapeutic protocol and data collection concerning safety and efficacy are mandatory for both cohort and nominative ATU.

This law also introduced the concept of "temporary recommendation of use" ("*recommandation temporaire d'utilisation*" - RTU) developed and published under the responsibility of the ANSM. The aim of RTU is to provide a framework for the prescription of a medicinal product beyond the indications of its MA when no other medicinal product with a MA or a cohort ATU is available for the considered indication. The development of RTU is possible when the ANSM considers the available data are sufficient to presume a favourable benefit risks ratio. Prospective data collection concerning safety and efficacy of the drug is mandatory when a RTU is published. In November 2012, the ANSM published a template²²² for the follow-up of patients and collection of data if RTU are available. In order to help the ANSM to prepare the development of RTUs for rare diseases, the Ministry of Health asked the Reference Centres in July 2012 to carry out an inventory of their prescriptions out of the MA of the medicinal products that could be eligible for RTU. The questionnaire was returned by 70% of the Reference Centres. The data were compiled by the ministerial authorities and sent in November 2012 to the ANSM which is now exploiting them.

In hospitals, Temporary Treatment Protocols ("*Protocoles temporaires de traitement*" - PTT) may also be used to extend the indication for a drug or device with reimbursement permitted. Temporary Treatment Protocols are limited to expensive drugs used only in hospitals and registered on a special list.

In 2006, the law for the financing in 2007 of French Social Security system planned a derogative pathway for exceptional coverage of off-label use of medicinal products and of non-covered medical devices or services by the National Health Insurance²²³. Orphan or non-orphan medicinal products used off-label, medical devices or services intended for rare diseases are in particular concerned. The complete reimbursement is allowed for a limited renewable period by the Ministry of Health after the HAS has given a positive opinion. Since the law of the 29 December 2011 reinforcing the monitoring of safety of drugs and other healthcare products, the ANSM must publish a RTU before the HAS is allowed to advise the complete reimbursement of a medicinal product used off-label.

The ANSM also established a national public register of clinical trials on medicines conducted in France, which is regularly updated.

Other therapies for rare diseases

No specific information reported.

²²¹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p14)

²²² http://www.legifrance.gouv.fr/jopdf/common/jo_pdf.jsp?numJO=0&dateJO=20121122&numTexte=13&pageDebut=18412&pageFin=18414

²²³ Article L162-17-2-1 of the Social Security Legal Code.

Orphan devices

No specific information reported.

Specialised social services

Respite care services are available for patients whose care is demanding temporary relief of their relatives: this is only partially reimbursed for some rare diseases. Therapeutic recreational programmes are available mostly within hospital organisations and patient organisations or local institutions, and are mostly fully reimbursed. Social assistance community centres ("*Centres communaux d'action sociale*" - CCAS), social assistants within hospital structures, and services provided by patient organisations all aim to assist the integration of patients with rare disease into daily life. These services are financed either by government or community budgets or patients' organisations. The AFM has a number of administrative, medical and social coordinators who assist families with their specific needs.

On 9 February 2010 an interministerial observatory was created to evaluate the accessibility of public buildings, housing, work places, transport and footpaths/roads to all persons.

1.10. GERMANY²²⁴

Definition of a rare disease

Stakeholders in Germany accept the European Regulation on Orphan Medicinal Products definition of a prevalence of not more than 5 in 10 000 individuals.

National plan for rare diseases and related actions

In the German health care system every patient is entitled to complete health care coverage consisting of preventive, diagnostic, therapeutic and rehabilitative measures. The medical care of patients is generally of high quality and the access to medical doctors and specialists is on a high international standard. There is no national plan for rare diseases in Germany at the moment, and there are no specific funds allocated to rare diseases in the health care system, although ad hoc funding for rare disease projects does exist.

However, the first steps are being made to establish a national plan for rare diseases. An in-depth evaluation of the situation of patients affected by rare diseases in Germany was published by the Federal Ministry of Health in August 2009. The study is entitled "*Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen in Deutschland*" ('Strategies for improving the health care situation of patients with rare disease in Germany'). The study analyses the current situation of care for persons with rare diseases in Germany from the perspective of various actors in the health care system by evaluating the perspective of public organisations, service providers and patient organisations on the basis of quantitative and qualitative surveys in the form of questionnaires, individual interviews and group discussions. In the process, the priority spheres for action in the areas of the general care situation, specialised forms of care, diagnosis, therapy, exchange of information and experience as well as research, are identified. This provides the basis for discussions regarding the first implications of implementing a national action forum as well as a national action plan for rare diseases in Germany. Subsequently, possible solutions for individual areas will finally be developed in co-ordination with existing and planned activities at EU level.

The Federal Ministry of Health in Germany initiated a national action league for people with rare diseases - *Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen* (NAMSE)²²⁵ – in Berlin on 8 March 2010. NAMSE is a co-ordination and communication platform comprising all key bodies and organisations. The following stakeholders are part of this platform and the steering committee: the Federal Ministry of Health, the Federal Ministry of Education and Research, the Federal Ministry of Labour and Social Affairs, the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth, the 16 Federal *Laender* (*federal states*), health insurance funds (sickness funds), associations of panel doctors, hospital associations, the Federal Joint Committee, medical societies, scientific societies, patient representatives, including the

²²⁴ The German Federal Ministry of Health can only verify the information and data which concern federal responsibilities. The information provided here is illustrative and not exhaustive, and that it is validated by the EUCERD Member State representative to the best of their knowledge.

²²⁵ <http://namse.de/>

National Alliance for Rare Diseases “ACHSE”. NAMSE is coordinated in a joint effort by the Ministry of Health, the Ministry of Education and Research and ACHSE.

This platform provides the basis for further concerted action, including the implementation of a National Action Plan on Rare Diseases. All partners, the major institutions and stakeholders of the German health care system, adopted a common declaration to improve the health situation for people with rare diseases in Germany. By this declaration all partners of the action league declare their willingness to contribute towards the implementation of the established goals through their active participation in the action league. One established goal is to contribute to implementing the Recommendation of the Council of the European Union. This includes the drafting of a National Action Plan for Rare Diseases and its implementation and monitoring as recommended in the EU Council Recommendation on an action in the field of rare diseases, the coordination of measures for improving the health situation of persons with rare diseases, supporting the establishment of centres of expertise, initiating pilot projects and further action in the field of rare diseases, and assembling initiatives and making all actors involved cooperate in a coordinated and goal-orientated manner to put patients’ care first. The process is organised in a steering committee and four working groups. Amongst others they try to identify ways how to improve the information on rare diseases, how to speed up the diagnosis of a rare disease, how centres of rare diseases could be structured, how to reach the experts and how research can more easily benefit the patients. At the end of this process the national action league for people with rare diseases will recommend different actions for the German National Action Plan for Rare diseases.

By the end of 2012, around 60-70 proposed measures had been discussed in a workshop with all members of the NAMSE working groups. In the context of the elaboration of the national plan, the objective is to adopt the proposed measures in 2013 by NAMSE and then to hand them over to the federal government which will adopt the plan.

Centres of expertise

The implementation of national centres of expertise in Germany is challenged by the decentralised, federal structure of the German health care system, since the provision of sufficient structural resources for health care is a matter solely concerning the *Laender* (federal states).

German legislation provides the basis for the *Ambulante Spezialfachärztliche Versorgung* (highly specialised outpatient care) for a limited number of diseases (see below), some of which are rare.

In order to improve further the care of complex diseases – in particular rare diseases – new opportunities were opened by the Act on Care Structures in the Statutory Health Insurance System (*GKV-Versorgungsstrukturgesetz – GKV-VStG*) that entered into force on 1 January 2012. It provides for the gradual establishment of a new specialist care sector aimed to achieve seamless care provision between outpatient and inpatient settings.

Specifically, highly specialised outpatient care can now be provided by both hospitals and non-hospital doctors (office-based specialists) on a high level and at the same conditions in terms of quality and remuneration (Social Code V, Section 116b).

Highly specialised out-patient care comprises the diagnosis and management of complex, hard-to-treat diseases that require special qualifications, interdisciplinary co-operation and appropriate equipment. They include rare diseases and conditions with correspondingly low case numbers such as:

- tuberculosis
- cystic fibrosis
- haemophilia
- malformations, congenital skeletal abnormalities and neuromuscular conditions
- serious immunological disorders
- biliary cirrhosis
- primary sclerosing cholangitis
- Wilson's disease
- transsexualism
- caring for children with congenital metabolic disorders
- Marfan's syndrome
- pulmonary hypertension
- short bowel syndrome
- caring for pre- and post-transplant patients and for living organ donors

The sector of highly specialised outpatient care is organised by the Federal Joint Committee (*Gemeinsamer Bundesausschuss, G-BA*) that fleshes out the relevant legal provisions through binding guidelines. This includes, particularly, the specification of diseases, scope of treatment, technical resources and staff required for service provision as well as referral requirements and quality assurance measures. The Federal Joint Committee (*Gemeinsamer Bundesausschuss, G-BA*) also can extend this list of diseases which has been stipulated by law (Social Code V, Section 116b).

The Federal Joint Committee (*G-BA*) is the supreme decision-making body of the so-called self-governing system of service providers and health insurance funds in Germany²²⁶. In the field of outpatient care for rare diseases provided by hospitals according to Social Code Book V, Section 116b, the *G-BA* has to regulate both the structural and personnel resources needed for outpatient care provided by both hospitals and office-based specialists. Consequently, all of these service providers are subject to the same staffing, equipment and regulatory/contractual requirements as well as special measures for quality assurance. Basically, access is free for service providers that prove compliance with the applicable requirements.

From now on, the Joint Committee will be able to broaden the catalogue of services and diseases in response to an application from one of its member organisations or the organisations on the Federal level that champion the interests of patients, also the self-help organisations of chronically ill and disabled persons.

In addition to the so-called 'Section 116b centres', other centres like social-paediatric centres (Social Code V, Section 119) or university clinics for outpatient care (Social Code V, Section 117) may also be involved in the treatment of rare disease patients. This applies also to specialised ambulatory care offered by authorized physicians in hospitals.

There are already several self-appointed centres for rare diseases in Germany²²⁷. However, these do not share a nation-wide concept and are not reviewed in respect of any specific quality criteria for rare diseases. Therefore, it falls to the NAMSE process to define and develop national framework conditions for centres and networks dedicated to rare diseases. This process is underway, with a number of meetings organised to discuss criteria and indicators for such centres. This also includes topics such as the setting up of registries and biobanks as it does the drafting of criteria and eligibility procedures for the certification of future centres. The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner, EUCERD member). The group decided in 2012 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

Registries

There are some registries for rare diseases in Germany, although there is no centralised accreditation or designation of these registries. The future rare disease action plan will consider the area of registries and a possible minimal data set to be applied. There is no public central clinical trial registry dedicated solely to rare diseases. However the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) which is funded by the Federal Ministry of Education and Research (BMBF) aims at registering all trials performed in Germany, including those for rare diseases. All federal states are obliged to register cancers, including rare cancers, in existing population based cancer registries. An analysis based on the Orphanet database identifies about 80 registries, most of them belonging to academic institutions. Some of these registries are implicated in international networks or covers the whole European region.

German teams contribute to European registries such as CompERA-XL, CWS-SoTiSaR, DOSAK, CEDATA-GPGE, EUROCAT, TREAT-NMD, EBAR, ENETS, EPICURE, EU-RHAB, EurIPFreg, EHDN, EIMD, EurIPFnet, E-IMD, EURIPEDES, European Alport registry, EuroDSD, EUROSCA-R, EUTOS, Kids Lung Register, KINDLERNET, NCL-Registry, PODONET, Register for rare myeloproliferative neoplasms, RetDis Database, and RegiSCAR, and generally to clinicaltrials.eu.

²²⁶ Physicians, dentists, hospitals and health insurance funds are represented in the *G-BA*. Since 2004 national groups representing patients were given the right to file applications and to participate in the consultations of the *G-BA*. The *G-BA* issues the directives/binding guidelines that are necessary for safeguarding medical service provisions. The latter aims to ensure that medical services for persons ensured under the statutory health insurance in Germany are adequate, appropriate and efficient. The *G-BA* issues directives and thus determines the benefit package of the statutory health insurance (*gesetzliche Krankenversicherung, GKV*) covering about 70 million people. The *G-BA* is responsible for reimbursement decisions in the statutory health insurance (*GKV*).

²²⁷ Listed in <http://www.orpha.net/national/DE-DE/index/zentren-für-se/>

Genetic testing and Newborn Screening Policy

On 1 February 2010, a law passed by the German Bundestag regulating genetic testing in humans officially entered into force. The Genetic Diagnostics Act (GenDG) establishes the prerequisites for genetic testing, and genetic analysis conducted in the framework of genetic testing and stipulates requirements for the use of genetic samples and data. It applies to genetic testing and genetic analysis on born human beings as well as on embryos and fetuses during pregnancy and to the handling of the genetic samples and genetic data obtained in the process for medical purposes, to clarify parentage as well as the insurance sector and working life. It does not, however, apply to genetic testing and analysis and the handling of genetic samples and data *inter alia* for research purposes. The Genetic Diagnostics Act seeks to prevent discrimination based on genetic characteristics, to protect human dignity and the right to informational self-determination and aims at providing binding standards for good genetic testing practice.

Since 2005 there has been a mandatory legalised screening program covering fourteen conditions: phenylketonuria, biotinidase deficiency, galactosaemia, MCAD deficiency, VLCAD deficiency, LCHAD deficiency, CPT1, CPT2, CAT deficiencies, maple syrup urine disease, glutaric aciduria type 1, isovaleric acidaemia, congenital adrenal hyperplasia and congenital hypothyroidism.

Newborn screening is a genetic test as defined in the GenDG. As such, it is subject to the exclusive right of medical professionals to practise medicine as well as the requirements for informed and written consent. The Joint Federal Committee - as the joint self-administration body representing health insurance funds, the medical profession and hospitals - specifies in a binding guideline the conduct of newborn screening and the diseases and conditions the screening for which is eligible for reimbursement by the statutory health insurance system.

Diagnostic tests are registered as available in Germany for 1754 genes and an estimated 1922 diseases in the Orphanet database²²⁸.

National alliances of patient organisations and patient representation

In Germany, the German National Alliance for Chronic Rare Diseases (ACHSE) is a network of more than 100 patient organisations of people living with a specific rare disease. Through ACHSE, rare disease patient organisations support each other, exchanging know-how so as to strengthen their influence in the political arena and improve the quality and duration of life of people living with a rare disease. ACHSE is an active member of EURORDIS and a member of its Council of National Alliances.

In Germany, health-related self-help groups and organisations are eligible for financial support from the statutory health insurance funds. A legislative reform (1 January 2009) has made access to funding easier and the distribution of the funding ear-marked by the statutory health insurance funds is guaranteed: this meant about €40 million in 2011.

The Ministry of Health currently supports different projects concerning the participation of patients with rare diseases at the Charité Berlin. One of these projects (2009 – 2011) dealt with the “Contribution of self-help groups/ patient organisations to the organisation of interfaces within the health care system”, aimed at improving patient participation and orientation. The Ministry of Health also supports other activities in the field of rare diseases such as conferences, brochures, workshops.

An important role is played in the regulation of the medical services of the German health care system by self-governing bodies such as patient associations: since 2004, national groups representing patients participate in the consultations of the Federal Joint Committee.

Sources of information on rare diseases and national help lines

Orphanet activities in Germany

The Orphanet portal on rare diseases is available in German²²⁹ and is widely used as a major information source on rare diseases in Germany. Since 2001 there is a dedicated Orphanet team in Germany, currently hosted by the Human Genetics department of the Hannover Medical School (MHH). This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was officially designated as the Orphanet national team for Germany by the Federal Ministry of Health in 2010. In 2010, the Orphanet-Germany national website was launched²³⁰. This German language page is maintained by the Orphanet-Germany team and features information, news and events specific to field of rare diseases in

²²⁸ Information extracted from the Orphanet database (December 2012): this information is not verified by the German Federal Ministry of Health.

²²⁹ www.orphanet.de

²³⁰ <http://www.orpha.net/national/DE-DE/index/startseite/>

Germany. Users can access the main Orphanet site in any of the five available languages, as usual, from this page.

Official information centre for rare diseases

There is no official information centre on rare diseases in Germany.

Help line

There is currently no official help line for rare diseases in Germany. However, ACHSE offers a privately funded help line for people living with a rare disease since 2006 and answers about 600 to 800 requests per year. The help line is also open for professionals, but not often addressed by them. The help line is financed solely with donations and through charity events.

Other sources of information on rare diseases

All medicinal products, including orphan medicinal products, are included in a database called PharmNet, run by the German Institute of Medical Documentation and Information (DIMDI) ensuring public access to package leaflet, summary of product characteristics (Fachinformation in German) and the assessment report (publicly accessible version).

On the first of January 2011 Section 42b AMG (Arzneimittelgesetz, Medicinal Products Law) came into force stipulating pharmaceutical companies and sponsors of clinical trials to report results of clinical trials to the federal higher authorities for purposes of publication in the public database PharmNet.Bund run by DIMDI²³¹.

The ACHSE website²³² provides a platform for information on rare diseases. This platform is a validated and patient-orientated source of information. It encourages patient organisations to improve their information continuously. ACHSE has also established a help line to inform patients and their families in particular those without a diagnosis or an established patient organisation.

The KINDERNETZWERK²³³ offers a service line for patients with rare diseases together with patient oriented online diseases descriptions. The KINDERNETZWERK additionally holds a database for registering parents with children suffering of rare diseases. Information on patient groups can also be found at the NAKOS website²³⁴ (The National Clearing House for the Encouragement and Support of Self-Help Groups). Other non-rare disease specific help lines are available to help patients understand the health care system.

Beside the above mentioned internet information sources for rare diseases there exist several informational websites for rare diseases run by e.g. patient organisations, learned societies and university institutions. Some (genetic) diagnostic labs also offer information about tested diseases in detail. Several other internet databases are offering information on common diseases which imply also information on rare diseases: DermIS (www.dermis.net) an internet based information system for dermatology (recently public funded by the Federal Ministry of Education and Research, now private funding by Bayer Health Care), ONKODIN (www.onkodin.de) with focus on hematological diseases, public funding, www.patienten-information.de (www.patienten-informationen.de) of the ÄZQ (Agency for Quality in Medicine) – an initiative of the Bundesärztekammer (German Medical Association) and the Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians) and others. The University Rostock, Albrecht-Kossel-Institut for Neurodegeneration is hosting the data-base www.selteneerkrankungen.de, mainly focusing on rare neurodegenerative diseases and the laboratories that are apparently qualified for diagnosis (Funding is unclear). There is also the Rare Metabolic Diseases Database which receives public funding from the German Federal Ministry of Education and Research, and is hosted by the Bielefeld University, Bioinformatics Department. It also represents a patient registry for rare metabolic diseases.

Good practice guidelines

For some rare diseases there exist practice clinical guidelines (i.e. cystic fibrosis, diagnostic of myopathy, congenital adrenal hyperplasia) from the AWMF (Association of the Scientific Medical Societies, *Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften*). In 2011 the Institute for Quality and

²³¹ protocol related data from clinical trials (<http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>), result related in the near future (<http://www.pharmnet-bund.de/dynamic/de/ergebnisberichte/index.htm>).

²³² www.achse.info

²³³ www.Kindernetzwerk.de

²³⁴ www.nakos.de

Efficiency in Health Care (IQWiG) published a rapid report (V 10-01) concerning the question “What type of evidence is currently being considered in the development of clinical practice guidelines for rare diseases?”²³⁵.

Training and education initiatives

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

The Centre for Rare Diseases Tuebingen (University Hospital Tuebingen) provides continued education for physicians since April 2011. The program is called the German Academy for Further Medical Training on Rare Diseases (FAKSE). The goals of the academy were: to educate practice-based physicians and clinicians on the matter of rare diseases in an interdisciplinary and illustrative fashion; to raise awareness for these disorders and provide physicians with methodologies and “Red Flags” for better recognition of RD; and to bring physicians in contact with relevant experts and patient organisations. Throughout its first year, FAKSE organised four training courses and has already trained 250 physicians. In 2012, two more courses on rare auto inflammatory diseases and rare tumours were held. Further courses for 2013 are already being planned. Before and beside this programme there exist also other possibilities for continued education for physicians concerning rare diseases.

National rare disease events in 2012

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

In Germany several events were organised to mark Rare Disease Day 2012, coordinated by ACHSE. These events took place in Bielefeld, Dessau, Essen, Flensburg, Halle, Hamburg, Köln, München, Nürnberg and Würzburg. On 28 February 2012, the Eva Luise Köhler prize for research on rare diseases was awarded²³⁶. On 29 February 2012 a political symposium on the theme “rare but strong together – finding better ways for people with rare diseases” was organised by ACHSE and attended by the German Minister of Health, Daniel Bahr, and the President of the German Medical Association. Expert panel discussions provided the opportunity for in depth discussion on a number of themes. On 29 February 2012, the 3rd Rare Disease Day Symposium organised by Orphanet Germany was held at the Hannover Medical School. More than 30 different support groups attended the event and manned the stands at the event, providing an opportunity to meet the 350 visitors about. Some patient organisations gave talks together with the professionals from the newly created centre of rare diseases of the Hannover Medical School. This year was also the first time that professionals from the pharma industry presented their activities in the field of orphan medicinal products.

Hosted rare disease events in 2012

Amongst the events hosted in Germany and announced in *OrphaNews Europe* were: 4th International Tuebingen-Symposium on Pediatric Solid Tumors (Tuebingen, 16-18 February 2012), International Meeting on Rare Diseases: Mechanisms and New Therapeutic Approaches (Freiburg, 22-24 February 2012), 5th International Conference on Ectodermal Dysplasia (ED2012) (Erlanger, 1-3 June 2012), 10th International primary hyperoxaluria workshop (Bonn, 22-23 June 2012), European Human Genetics Conference 2012 (Nurnberg, 23-26 June 2012), Retina International World Congress (Hamburg, 14-15 July 2012).

Research activities and E-Rare partnership

National research activities

In 2003, the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) funded ten networks of national academic groups, clinical centres, specialised laboratories and patients organisations for basic and clinical research for an initial three years. After a successful interim evaluation, nine of the networks for rare diseases were funded for another two years. The budget of this rare disease research programme was €31 million.

²³⁵ https://www.iqwig.de/download/V10-01_Executive_Summary_Evidence_for_guidelines_on_rare_diseases.pdf

²³⁶ http://www.achse-online.de/cms/was_tut_achse/forschung_vorantreiben/koehler_forschungspreis.php

In 2007, the BMBF opened a new funding programme on rare diseases research with a substantial increase in budget to €24 million for the first 3 year period and a possible extension of the maximum funding duration of 3 times renewable 3 year periods for new networks. Starting in October 2008, 16 networks are currently being funded. Six of these are extensions of previously funded networks, while the other 10 networks are new. In 2010, the networks have been granted €6 million additional funds for investments in shared research equipment, most notably next generation sequencing. In September 2010, a new call for proposals for the possible extension of the 10 networks which started in 2008 and the creation of new networks was published. After the evaluation of 39 proposals by a review board of international rare disease experts, the BMBF has selected 12 networks for funding starting in 2012 with more than €21million for three years.

Additional funding of rare disease research is ongoing in other funding initiatives of the BMBF such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials and others with about €20 million in 2011. All these activities are funded within the framework programme "Health research". In co-operation with the Federal Ministry of Health, the BMBF assumes responsibility for the programme which is financed with funds from the BMBF.

The *Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen*, a foundation of the former First Lady and the former president of the Federal Republic of Germany, is dedicated to patients with rare diseases and supports research projects into rare diseases annually since 2006.

Regional sources of funding are also available.

Participation in European research projects

German teams participate, or have participated, in European research projects for rare diseases including: ALS-degeneration, ACADEMIC GMP, AIPGENE, ALPAMAN, AUTOROME, ANTEPRION, BIOMALPAR, BNE, CAV-4-MPS, CRANIRARE, CURE-FXS, CHD PLATFORM, CILMALVAC, CUREHLH, CURE-FXTAS, DSD-LIFE, DRUGSFORD, DEMCHILD, DARTRIX, EDEN, EMVDA, EMINA-2, ENRAH, ENCE-PLAN, EURADRENAL, ENS@T, EUCILIA, EUNEFRON, EURIPFNET, EUROBONET, ESPOIR, EURENOMICS, EUROBFNS, EUROSDS, EURO-CDG, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROSCA, EURO-SCAR, EUROTRAPS, EURORETT, EUROMOTOR, EUR-USH, EuroDBA, EUROSPA, ERMION, EuPAPNet, EUBNFS, EURO-CGD, ELA2-CN, EMINA, EPINOSTICS, EUREGENE, EUROPEAN LEUKEMIA NET, EMSA-SG, ESDN, FNAIT, FASTEST-TB, GAPVAC, GETHERTHAL, GENEGRAFT, GENOMIT, HEART-DM, HMA-IRON, HAE III, HDLOMICS, HUE-MAN, HMANASP, IPF-AE, IMPACTT, INNOVALIV, INTREALL, IMMOMECC, INTHER, KINDLERNET, LEISHDRUG, NEUROMICS, MANASP, MITOTARGET, MTMpathies2, MYORES, MIMOVAX, MOLDIAG-PACA, NEUROSIS, NSEuroNet, NEUTRONET, NEMMYOP, NEWTBDRUGS, PULMOTENSION, OVCAID, OPTIPS, OVER-MyR, OPTATIO, OSTEOPETR, PPPT-MJB, PYRAMID, PADDINGTON, PODONET, PEMPHIGUS, RD-Connect, RD PLATFORM, RevertantEB, RAREBESTPRACTICES, RHORCOD, RATSTREAM, RARE-G, RISCA, Splice-EB, STRONG, SKIN-DEV, TIRCON, TAIN, TARGET-CdLS, TRANSPOSMART, WHIM-Thernet, WHIPPLE'S DISEASE and TB-VIR.

E-Rare

Germany is a partner of the E-Rare project, represented by the BMBF and the Project Management Agency of the German Aerospace Centre (*PT-DLR*). Germany participated in the E-Rare joint transnational calls in 2007, 2009 and 2011 and funds the participating German research groups of 35 transnational research projects with a total of about €10 million. Germany participated in the 4th Joint Transnational Call in 2012 with German research groups participating in 10 of the 11 projects selected for funding of about €3.4 million.

IRDiRC

The Federal Ministry of Education and Research (BMBF) is a committed member of IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

No specific information reported.

Orphan medicinal product incentives

Orphan medicinal products are also exempted from the mandatory rebate to the statutory and private health insurance funds on sales of products outside the German maximum reimbursement prices (*Festbeträge*) system, though evidence for the need of this exemption must be provided by the company²³⁷. See further under section "Orphan medicinal product reimbursement policy".

²³⁷ Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)

Orphan medicinal product market availability situation

No specific information reported.

Orphan medicinal product pricing policy

All orphan medicinal products are reimbursed directly after market authorisation. As the German maximum reimbursement prices scheme (Festbeträge) normally does not cover orphan medicinal products, they were excluded from any on reimbursed prices. Only generic products and those considered to belong to the same pharmacological or therapeutic group can be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, for every new drug with patented or non-generic substances a binding ex-factory price based on the value of the drug have to be negotiated on Federal Level. This is carried out by the Federal Association of Sickness Funds and the manufacturer. If no agreement can be achieved, the price is set by arbitrage committee, in which both contract parties are represented. For the first 12 months following marketing authorisation each new drug is still reimbursed at the full price set by the manufacturer. Mandatory Price Negotiations have been introduced by the Act for the New Order for the Drug Market in Social Health Insurance (AMNOG). According to this law, previous to price negotiations the value of the drug is evaluated. The manufacturer issues a Dossier when they enter the market. It is assessed by the German Institute for Quality and Efficiency in Health Care (IQWiG). The Federal Joint Committee (G-BA) appraises and decides on the added value of the drug compared to standard therapy.

Orphan medicinal product reimbursement policy

Once authorised at European level, all orphan medicinal products are fully reimbursed by the statutory health insurance (GKV). Until 31 December 2010, all newly authorised drugs could be put on the marketplace without any restrictions on reimbursed prices. Only generic products and those considered to belong to the same pharmacological or therapeutic group could be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, the act on new regulations for the drug-market (AMNOG) is mandating that all drugs with patented substances are subject to a cost/benefit analysis followed by a price negotiation. However, while this procedure that is limited to 12 months following marketing authorisation, is running, the product is still reimbursed at the price set by the manufacturer. Orphan medicinal products authorised by EMA under EU-regulation 141/2000 with an annual turnover below €50 million are exempted from the benefit assessment, because the benefit is taken as granted. Still, price negotiations are mandatory also for these drugs.

Other initiatives to improve access to orphan medicinal products

Irrespective of the prevalence of the disease, the off-label use of drugs is reimbursed by the statutory health insurance (GKV) on the following conditions: the drug will be used to treat a life-threatening or fatal disease; there is an absence of pharmaceutical therapy with a marketing authorisation in Germany; and there is scientific evidence of positive therapeutic effects²³⁸.

In Germany, as in many other European countries, it has been basically possible to administer promising medicinal products for severely ill patients before authorisation in case no alternatives exist. In 2005, on the basis of Art. 83 of the Regulation (EC) No 726/2004 the German government implemented general rules providing such medicinal products in form of so-called Compassionate Use Programmes in Section 21 sub-section 2 no. 6 of the German Medicinal Products Act. In 2009 it was added that the provision of a medicinal product in such cases has to be free of charge. An ordinance, coming into force 2010, contains special regulations for the proper procedure of Compassionate Use Programmes. An overview on Compassionate Use Programmes confirmed by the Federal Institute for Drugs and Medical Devices (BfArM) is available on the website²³⁹. Once authorised, all orphan medicinal products are fully reimbursed by statutory health insurance.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

²³⁸ Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)

²³⁹ www.bfarm.de

Specialised social services

No specific activity reported.

1.11. GREECE

Definition of a rare disease

Stakeholders in Greece generally accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals; however no official definition has been proposed or accepted.

Health care professionals and stakeholders, for the precise evaluation of the burden of a rare disease on public health, propose the use of supplementary indices such as the annual rate of births of affected newborns for genetic diseases with short survival and/or population specificity and age group prevalence for diseases prevailing either in children and adolescents or in adults and old patients.

This definition is for discussion in the agenda of the steering committee working on the final revision on national plan for RD.

National plan/strategy for rare diseases and related actions

A commission composed of government officials, health professionals and patient representatives was formed in 2007 following requests by the Greek Alliance for Rare Diseases (PESPA) to help draft the Greek National Plan for Rare Diseases. PESPA members presented a draft to the Committee, which was then modified by officials of the Greek Ministry of Health and Social Solidarity to the format of the current Plan. An outline for this National Plan of Action for Rare Diseases (to run over the period 2008-2012²⁴⁰) was presented by the Greek Minister for Health in February 2008: this document identified and outlined eight strategic priorities:

- Acknowledgement of the specificity of rare diseases (registration on the list of chronic long-term disorders),
- Increase the knowledge of the epidemiology of rare diseases and establish a National Registry of Rare Disorders,
- Develop information for patients, health professionals and the general public concerning rare diseases,
- Upgrade services for diagnosis, therapy and rehabilitation of rare diseases patients (training for health care professionals to improve diagnosis and access to quality health care),
- Organise screening and access to diagnostic tests,
- Promote research and innovation regarding rare diseases and specifically effective new therapies,
- Respond to the specific needs of people living with rare diseases,
- Generation of an integrated platform for action in the field of rare diseases at a national level and the development of European partnerships.

The provisions of the Greek National Plan for Rare Diseases (2008-2012) were discussed in detail during the Greek National Conference on Rare Diseases²⁴¹ co-organised by the Greek Alliance for Rare Diseases (PESPA) and EURORDIS, - in Athens (26-27 November 2010) in the framework of the Europlan project. The priorities listed during the conference included: the need for a legal framework of the National plan and a steering committee, the need for a policy to establish centres of expertise, the need to complete the map of diagnostic laboratories, the need to establish universal access to orphan medicinal products, the need to officially recognise the specialty of Clinical and Laboratory Genetics, the need to fully reimburse diagnostic tests (including molecular diagnosis), the need for therapy and rehabilitation, the need for price adjustment of orphan medicinal products in order to continue to be available in the Greek market, the need for funding of rare disease research and the need for more information on rare diseases in Greece.

Although an initial estimate for the budget required was made, no funding has been officially allocated to the National Plan of Action for Rare Diseases, and none of the eight strategic priority actions have yet started. As of yet, there is no legal framework for the Plan so no progress has been made.

²⁴⁰ http://www.vgeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf

²⁴¹ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report%20Greece%20EUROPLAN%202010.pdf (accessed 28/01/2011)

In fact, most of the objectives of the proposed national plan of action for RD are or could be incorporated in the existing structure and function of Greek national health system (GNHS). Implementation of strategic priorities for RD is coordinated by the Ministry of Health and mainly by the Hellenic Centre of Disease Control and Prevention (KEELPNO) - alongside their official role in surveying and prevention of common and rare diseases.

In 2010 the Advisory Scientific Committee for Rare Diseases appointed by KEELPNO together with the office for RD of KEELPNO started to implement the main priorities of national plan for RD defined in the scope of the Europlan project that are incorporated in the Greek NHS. The program started in 2011 with two main objectives: i) to develop a national registry of rare diseases and ii) to identify the expertise centres (CEs) involved in the care of patients with rare diseases, within the Greek National Health System (NHS).

The Second EUROPLAN Conference, organised by the Greek Alliance for Rare Diseases, on 1 December 2012, was met with great success, with the acceptance and active participation of all the involved stakeholders, as well as an impressive attendance by patients from all over the country. The conference was organised by PESPA with the support of EURORDIS, and was held under the auspices of His Excellency, the President of the Hellenic Republic, Mr. Karolos Papoulias. During the Conference, four working groups were created, in which various stakeholders from EOF, KEELPNO, IFET, SFEE, as well as patients, participated. The principle subjects worked upon were predetermined by the EUROPLAN program: Patients' Access to their Diagnosis and Medical/Pharmaceutical Care; Social Security Rights for Patients with Rare Diseases; Reference Centres for Rare Disease; and Rare Diseases Registries in Greece. The results of the working groups focused on present-day problems for Greek patients with rare diseases, changes that need to be made, as well as new suggestions, shaping a complete plan of action for rare diseases, which will form the basis of the final report that will be sent from Greece to the European Parliament. For example, some of the actions suggested during the conference will be implemented in the official report: establishment of already existing clinics as Reference Centres for Rare Diseases and creation of new ones (i.e. Children's Hospital, Sismanoglio, Evangelismos); participation of patients in the decision-making process for subjects that have to do with their medical/pharmaceutical care; establishment of the mandatory use of the ICD10 codification for rare diseases in the electronic prescription process, so that fully measurable data can be gathered for every disease; and cooperation of all registry stakeholders in Greece, for the creation of a common network.

In November 2012 a Steering Committee for Rare Diseases was appointed by the General Secretary of the Ministry of Health to review and supplement the plan proposed during the Europlan meeting in 2009 and submit it to the Ministry for discussion, adoption and implementation.

To place these developments in context, health services already provided by Greek National Health System (NHS) can be classified in two main types. The first covers children and adolescents aged 0-19 years old and the second adults and older patients (over 20 years old). In the first type, primary health care is provided by family pediatricians and in the second by internists and physicians with basic specialties in Internal Medicine. For patients with life threatening disease and chronic debilitating diseases, such as rare diseases, hospital care is provided in two levels: for children and adolescents in paediatric clinics of rural hospitals for common and non severe diseases and University Departments of Paediatrics and Children Hospitals operating divisions of pediatric specialties, subspecialties, special reference units and basic and research laboratories. For adults and older patients' hospital care is provided in general regional hospitals and in University Hospitals and Referral General Hospitals with departments, divisions and special referral units, supported by routine and specialised research laboratories.

In both branches of Greece's NHS the care of patients with rare diseases is multidisciplinary and homogeneous to that of patients with relative common diseases of similar pathogenesis.

Special units in Research Institutes and private laboratories contribute to pre and post natal diagnosis for a number of rare diseases.

Other national actions related to rare diseases include:

- The National Programme for haemoglobinopathies (covering thalassaemia and sickle cell diseases) which includes carrier detection, prenatal diagnosis, patient diagnosis and therapy. This Programme is split into two areas, a prevention programme organised in the late 1970s and implemented in the 1980s, and a treatment programme implemented gradually in the 1970s
- The National New Born Screening (NBS) program concerning ~ 98% of neonates born all over Greece.

Centres of expertise

Within the national health system special units providing expert services for groups of a limited number of diseases including specific rare diseases/groups of rare diseases have been organised during the past few decades. The Hellenic Centre for Disease Control and Prevention (KEELPNO) started to collect data on the

nature and activities of these units and aims to complete collection in 2012. Greece is working to provide better access to treatment for rare disorders, including the accreditation and creation of centres of expertise for rare disorders.

By the end of the 2011 the multidisciplinary centres of expertise (basically day care clinics) for the management of thalassemia, cystic fibrosis, neuromuscular disorders, hereditary bleeding diseases and primary immunodeficiencies were identified and evaluated. Identified centres of expertise include:

- Thalassemia: 15 centres (Two follow more than 400 patients, four 150-200 patients and nine 70-150 patients)
- Cystic Fibrosis: 3 centres (2 for children and adolescents and 1 for adults)
- Neuromuscular Diseases: 6 centres (2 for children and adolescents , 2 for adults and 2 for all ages)
- Hereditary Bleeding disorders: 4 centres (3 for adults and 1 for children and adolescent) and
- Primary immunodeficiency: 2 centres for children and adolescents

These centres of expertise collaborate with the follow expert laboratories.

- The Laboratory of Medical Genetics of the University of Athens, "Agia Sophia" Children Hospital, for the molecular pre and post natal diagnosis of thalassemia, cystic fibrosis, and neuromuscular diseases; it also serves as national reference laboratory for a number of genetic diseases.
- The laboratories of a) Genetic Neurological Diseases and b) Muscle pathology of the Department of Neurology, Athens University serving also as the National Reference Laboratory.
- The national Thalassemia Prenatal Diagnosis Centre covering 60-70% of prenatal diagnosis of thalassemia. In 2012, this was nominated as a Reference Centre and was renamed to "Reference Centre for the Prevention of Thalassemia and Sickle Cell Disease", Laikon General Hospital.
- The Department of Plastic Surgery-Microsurgery and Burn Centre of General Hospital of Athens "G. Gennimatas" was nominated as Reference Centre Melanoma, in 2012.

According to the evaluation of new Scientific Committee for Rare Diseases, certain centres of expertise involved in the management of these five diseases/groups of rare diseases, fulfil the EUCERD Recommendations on Quality Criteria for National Centres of Expertise for Rare Disease in Member States. Data has been collected in 2012 concerning centres of expertise but has not yet been evaluated.

Registries

There is currently no national registry for rare diseases in Greece. One of the main tasks of the KEELPNO and the new steering committee for rare diseases is to set up a national registry, according to the international standards. A pilot registry which started in 2011 is in progress. Creation of a registry for Registries to collect all available for RD registries in Greece was discussed at the second European conference in Athens, KEELPNO proposed to undertake this task.

In the absence of a national registry for rare diseases, scientific societies covering rare diseases, appointed working groups which, in collaboration with respective centres of expertise and patients organisations, have created registries for a number of rare diseases. Up to now the Scientific Committee on rare diseases reviewed and evaluated data collected and registered for thalassemia, cystic fibrosis, neuromuscular disorders, hereditary bleeding diseases and primary immunodeficiencies²⁴².

These registries do not receive national financing. Greek teams contribute to the European registries EUROCARE CF and EIMD.

Neonatal screening policy

Neonatal screening covering around 98% of neonates in Greece and is provided by the Institute of Child Health, Athens, for congenital hypothyroidism, phenylketonuria, G6PD deficiency and galactosaemia. Recently, the neonatal screening is expanding in the private sector covering a number of inborn errors of metabolism, cystic fibrosis, adrenal hyperplasia and biotin deficiency, as well as screening for the early diagnosis and treatment of congenital deafness. Data on the extended neonatal screening program in regard to efficacy and neonatal population coverage are not yet available. The national policy of neonatal screening program was not changed

²⁴² Two studies on Thalassemia and Hemoglobinopathies Registry have been recently published. The study group of hemoglobinopathies of Hellenic Hematology Society: Voskaridou E et al. A national registry of Hemoglobinopathies in Greece. Ann Haemat. publ. on line 19 APR 2012; the study group on Thalassemia of the Hellenic Pediatric Haematology society: Ladis V. et al. Thirty years experience in preventing hemoglobinopathies in Greece. Eur Jour Haematol. In press

in 2012 in the Greek NHS, a Ministerial Decision for the standardisation of the process of Development of execution of the NBS was launched.

Genetic testing

Genetic testing is carried out in different laboratories specialising in the diagnosis of different rare diseases. There are neither official reference laboratories nor guidelines. Tests are reimbursed through insurance (public and private) schemes and genetic testing is possible abroad. Genetic tests provided by special laboratories of the Greek NHS fulfil European guidelines.

Diagnostic tests are registered as available in Greece for 125 genes and an estimated 204 diseases in the Orphanet database²⁴³.

National alliances of patient organisations and patient representation

PESPA is an umbrella non-profit organisation established in 2003, by health professionals and presidents of 20 rare disease patient associations (national or regional) with the help of EURORDIS. PESPA organised in 2012 events for Rare Disease Day 2012 as well as the Europlan 2 conference on 1 December 2012 to discuss the national plan for rare diseases. In 2012 PESPA created a "Medical Support Fund for financially frail patients with Rare Diseases" to support in the current economic context families when they cannot receive support from their insurer.

In Greece, numerous national (Pan-Hellenic) patient organisations exist mainly for the more prevalent rare diseases. They have their own websites and are members of the related International and European federations. The Hellenic Thalassaemia Federation, the Association of Patients with Haemophilia, the MDA Hellas and the Society of Cystic Fibrosis are some of the indicative examples. In addition to national, there is also a considerable number of patients and parent-patient associations for rare diseases that autonomously organise their activities and conferences.

Alliances of friends of patients with rare diseases or group of rare diseases also exist. Few of them as the association of Friends of Children with Cancer "ELPIDA" and "FLOGA", MDA Hellas, Friends Association of Children with Chronic Rheumatoid Diseases are amongst the organisations which provide funding for the organisation and functioning of centres of expertise. ELPIDA donated to the "Aghia Sophia" Children's Hospital a modern and well-equipped Wing, "The Paediatric Oncology Unit Marianna Vardinoyiannis –ELPIDA", for the multidisciplinary care of children and adolescents with cancer; the new Wing has a capacity of 126 beds and started operating in January 2011.

There are currently no public funding schemes to support RD patient organisations activities in Greece.

Sources of information on rare diseases and national help lines

Orphanet activities in Greece

Since 2004 there is a dedicated Orphanet team in Greece, currently hosted by the Institute of Child Health initially by the Department of Genetics (2009) and recently by the department of Enzymology and Cellular Function (2012). The team was designated as the Greek national Orphanet team by the Ministry for Health and Social Solidarity in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. Greece participates in the Orphanet Joint Action and the Orphanet Greece national website in Greek was launched in 2011²⁴⁴.

Official information centre for rare diseases

There is no official information centre for rare diseases in Greece apart from Orphanet

Help line

There is no official government-supported help line for rare disease information in Greece; some services, mainly voluntarily are offered by PESPA's members who provide psychological support and a wide range of general information to patient and their families.

²⁴³ Information extracted from the Orphanet database December 2012.

²⁴⁴ <http://www.orpha.net/national/GR-EL/index/%CE%B1%CF%81%CF%87%CE%B9%CE%BA%CE%AE-%CF%83%CE%B5%CE%BB%CE%AF%CE%B4%CE%B1/>

Other sources of information

The websites of PESPA, Institute of Child Health, KEELPNO, scientific and patient societies and associations for RDs offer information on rare diseases and a list of some rare diseases in Greek. Every specialised unit produces information leaflets for the disease(s) of its expertise.

Good practice guidelines

Some scientific societies have published or renewed guidelines for specific rare diseases in local professional journals. All centres with expertise in rare diseases follow the international guidelines. There are national guidelines for thalassaemia.

Training and education initiatives

Rare diseases is a topic included in the general curriculum of undergraduate and postgraduate studies of Medical Schools in Greece and is basically addressed in the training for specialities and sub-specialities in Paediatrics and Internal Medicine. Scientific societies also organise courses and workshops in order to educate physicians, nurses and students on specific rare diseases.

National rare disease events in 2012

The Greek Alliance for Rare Diseases (PESPA) organised a series of events with the subject of "Rare but Strong Together" to mark Rare Disease Day 2012.

Members of the Greek Alliance for Rare Diseases, volunteers and the Greek Women Guides Association distributed leaflets regarding Rare Diseases in general as well as Rare Disease Day specific ones during the whole week around Rare Disease Day 2012. Throughout the month of February, Greek TV channels will broadcast a video spot regarding Rare Disease Day 2012, as well as a radio spot for radio stations, with a series of interviews and articles regarding rare diseases for the press. Four different Bicycle Races will be held in Ptolemaida, Thessaloniki and Athens, in order to raise awareness and celebrate Rare Disease Day 2012.

A Second European Conference was organised by PESPA on 1 December 2012. A range of stakeholders were present for the conference.

Hosted rare disease events in 2012

A meeting entitled "Molecular Genetic Diagnostic Tests" at the Medical School of the University of Patras on 3 February 2012. As in previous years a considerable number of scientific events, national and international conferences and meetings, were held in Greece concerning rare diseases.

Research activities and E-Rare partnership

National research activities

The General Secretariat for Research and Technology (Ministry of Education, Life Long Learning and Religious Affairs) has been funding research projects coping with all aspects of rare diseases (rare cancers included) in the framework of "biomedical research". However, there are no specific programmes for rare disease research and thus, it is very difficult to determine the funding allocated to rare diseases research only.

Participation in European research projects

Greece participates, or has participated, in European rare disease research projects including: BIOMALPAR, BNE, EPINOSTICS, EUROGLYCANET, ENCCA, EUROPEAN LEUKEMIA NET, EVI-GENORET, GEN2PHEN, GETHERTHAL, HDLOMICS, IPF-AE, ITHANET, MYASTAID, NEUROPRION, RDCONNECT and TRANSPOSMART.

E-Rare

Greece, through the General Secretariat for Research and Technology (GSRT), participated in the 2nd Joint Transnational Call of E-Rare-1. In this context, one project coordinated by a Greek team (with a total funding of around €262,000) was approved following peer-review evaluation and is in progress. Greece currently participates in E-Rare-2, and is represented by two institutions: GSRT and the Hellenic Center for Disease Control and Prevention (KEELPNO). GSRT participated in the 3rd Joint Transnational Call launched in 2011 with the amount of €200 000: two Greek teams were approved for funding after the evaluation of the call. Greece did not participate in the 4th Joint Transnational Call in 2012.

IRDiRC

The GSRT as a member of the E-Rare group of funders joined the IRDiRC in 2012.

Orphan medicinal products

The Greek National Organisation for Medicines (EOF²⁴⁵) ensures the public health and safety of all medicinal products, including orphan medicinal products. Orphan medicinal products that are not found on the market in Greece are imported by the Greek Institute of Pharmaceutical Research and Technology, and transferred to the patients requiring these drugs. A procedure for the compassionate use of orphan medicinal products (OMP) is in place

Orphan medicinal product committee

No specific information reported.

Orphan medicinal product incentives

No specific information reported.

Orphan medicinal product market availability situation

The following procedures are in place in Greece to ensure access to orphan medicinal products for patients with rare diseases. Orphan medicinal products authorised by the EMA are officially certified by the EOF (National Organisation for Medicines), before launched on the market after the blue box is issued by EOF. Orphan medicinal products authorised by the EMA or FDA but not launched in Greece (not included in price bulletin) can be imported through IFET (Institute of Pharmaceutical Research and Technology) if prescribed by a doctor and approval by EOF. This process provides access to any medicinal product orphan or not, for any individual patient or groups of patients according to specialist doctor's prescription.

The following orphan medicinal products are available in Greece: Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Ceplene, Cystadene, Diacomit, Elapraxe, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Firdase, Glivec, , Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Onseno, Orfadin, Pedeia, Peyona, , Prialt, Replagal, Revatio, Revlimid, Revolade, Rilnocacept, Regeneron, Savene, Siklos, Soliris, , Sprycel, Tepadina Tasigna, Thalidomide Celgene, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Yondelis, Zavesca. Prolastin, Paser Granules, Lioresal Intrathecal, Treanda, Ammunal, Cafcit, Cystagon, Depocyt, Dacogen, Ontak, Digibind, Flolan, Mylotarg, Riastap, Cyanokit, Lipoderm Patch, Sulfamylon Solution, Alkeran for Injection, Adagen, Oncaspar, Elmiron, Folotyn, Mycobutin, Rifadin, Leukine, Vumone for injection, Xenazine, Thiola, Syprine, Zolinza, Galzin, Viprid Gliolan, Mercaptopurine Nova, Plenadren, Signifor, Tobi Podhaler, Votubia, Vyndagel.

Of the orphan medicinal products authorised by the EMA, 43 are readily available on the Greek market, whereas 14 more are imported by the Greek Institute of Pharmaceutical Research and Technology. The remaining ODs could be imported on request by the Greek Institute of Pharmaceutical Research and Technology.

Lists of orphan medicinal products authorised at European level which are certified by the EOF and launched on the market in Greece, or not launched on the market but able to be imported by IFET if prescribed by a doctor and after approval of the EOF is available via the Orphanet Greece Country Site:

- a list of orphan medicinal products launched in Greece (included in price bulletin)²⁴⁶,
- a list of orphan medicinal products authorised by the EMA and imported by the IFET are available²⁴⁷,
- a list in addition to the list of the orphan medicinal products authorised by the FDA and imported by the IFET²⁴⁸.

The Greek Alliance of Rare Diseases (PESPA) expressed in 2012 the anxiety of Greek patients with rare diseases, as they are worried for the access to new medicines as quickly as it is possible after the authorisation of an orphan medicinal product. The main reason for not having a quick and easy access is the delay of giving a price to the orphan medicines as the Ministry of Health and EOF follow the same way for all medicines. There is no differentiation in the process between orphans and ordinary medicines and that means huge delays in pricing procedure. PESPA is asking, orphan medicines to be handled for pricing as quickly as possible exactly after the code number and the "blue box" for the marketing of the orphan medicine has been issued by EOF. PESPA tried to give their reasoning to the Prime Minister Antonis Samaras and the Minister of Health, Mr. Andrea Lykourantzou and explain the necessity for giving prices to orphan medicines as quickly as possible, as deterioration in the health of patients is unavoidable. PESPA argues that the deterioration of the health of

²⁴⁵ <http://www.eof.gr>

²⁴⁶ http://www.orpha.net/national/data/GR-EL/www/uploads/ORPHANS_EOF.pdf

²⁴⁷ http://www.orpha.net/national/data/GR-EL/www/uploads/ORPHANS_EMEA.pdf

²⁴⁸ http://www.orpha.net/national/data/GR-EL/www/uploads/ORPHANS_FDA.pdf

these patients, in addition to the price overcharge (if imported via IFET), will cost much more to the state because the necessary hospitalisation, consultations and other effects.

Orphan medicinal product pricing policy

No specific information reported. Medicinal products pricing policy in general was under continued revision in 2012. During 2013 the same pricing policy is continuing.

Orphan medicinal product reimbursement policy

All antineoplastic and immunomodulatory agents (29 drugs from the relative list of the *Orphanet Report Series: List of Orphan Drugs in Europe, January 2011*²⁴⁹), plus one drug for myoclonic epilepsy (Diacomit), one for cystic fibrosis (Cayston), one for beta-thalassemia (Exjade), one for Wilson disease (Wilzin) and two for Gaucher's disease (Vpriv and Zavesca) are 100% reimbursed (a total of 35 drugs). For the rest (26 drugs), some are 100% reimbursed, whereas some are reimbursed at around 90%.

Other initiatives to improve access to orphan medicinal products

There are currently no programmes to facilitate access to Orphan medicinal products. The Greek Alliance PESPA has put in place some awareness raising campaigns concerning orphan medicinal products.

Other therapies for rare diseases

Bone Marrow Transplantation is available at the paediatric Oncology Unit, Marianna Vardinoyiannis "ELPIDA", at the Aghia Sophia Children's Hospital, Athens.

Orphan devices

No specific information reported.

Specialised social services

Patients have limited access to respite care services, but these are not specifically for rare disease patients. The patients sometimes have to financially contribute to these services which are run by national institutions, patient associations and non-governmental organisations. A few therapeutic recreational programmes are available, organised by the same types of organisations, and the patient must also financially contribute to this. Limited help with household chores, psychological support, help with shopping and mobility assistance can be sought by patients with special needs (suffering from rare diseases or not) and are provided by local authorities or NGOs. PESPA provides some psychological support (with the help of professionals who are voluntary) to patients with rare diseases and their families.

1.12. HUNGARY

Definition of a rare disease

Stakeholders in Hungary accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

A decree of the Ministry of Health established the National Rare Disease Centre (NRDC) in Hungary on 11 November 2008 as a part of the National Centre for Healthcare Audit and Inspection (OSZMK) by modifying its foundation deed. The National Centre for Healthcare Audit and Inspection was a part of the National Public Health Institute, and was empowered to investigate quality related issues in health care, public health consequences of health care operation, and to initiate interventions if needed. Due to the restructuring of the national public health institutions, OSZMK was disbanded on 30 April 2011. The National Institute for Health Development (OEFI) became the new host organisation, which is subordinated to the Chief Medical Officer and is a part of the central public health institutions. The continuation of the NRDC operation has been ensured by the modification of the foundation deed of OEFI.

²⁴⁹ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

The NRDC participates in preparation of recommendations for Governmental Health Authorities in the following ways:

- It elaborates its own data collecting technology and co-operates with other stakeholders in order to obtain rare diseases related data and to prepare indicators;
- It defines public health indicators for rare diseases;
- It initiates the elaboration of rare disease guidelines and carries out the audit projects;
- It maintains the national database of rare diseases specialised health care providers;
- It contributes to the assignment of national centres of expertise and their participation in European networks;
- It facilitates the establishment and operation of the quality management programs for the Hungarian rare diseases laboratories;
- It facilitates the application of e-health in rare disease related care;
- It initiates the rare diseases teaching programs launching in the universities;
- It participates in the work of national agencies responsible for orphan medicinal product and orphan medical device legislation;
- It supports the improvement of the availability of special social services for rare disease patients;
- It supports the effective primary preventive program;
- It evaluates the effectiveness of the rare diseases screening programs;
- It facilitates rare disease research projects, both national and the international co-operations;
- It contributes to the development of collaboration between governmental bodies, health care providers and patient organisations;
- It supports the Hungarian participation in the European rare diseases projects;
- It initiates programs, which contribute to the improvement of the perception of rare diseases among the general public;
- It co-ordinates the elaboration and monitoring of national policy on rare diseases;
- It reports on the Hungarian achievements regularly.

The NRDC is supported by an advisory group; the member experts were appointed by the Chief Medical Officer. Its members are from the four medical universities (the Hungarian Medical Universities' representatives to the national advisory group are nominated by the deans), governmental institutions, and patient organisations. This group has a key advisory function of strategic planning, but does not have influence and control on the implementation of the decisions made.

The NRDC is assembling a National Plan Organising Committee by supplementing the current expert committee with representatives of sectors such as government and industry and the patient groups. The Ministry designated a competent, responsible Head of the expert committee, authorised to make decisions, to lead the development of the National Plan.

The former IT centre facilities are under reconstruction for the systematic analysis of the hospital and outpatient discharge records of rare diseases patients (for rare diseases which have their own ICD10 code), as well as laboratories, research programmes and patient groups.

The NRDC also works with the National Rare Disease Research Coordination Centre established in 2009 under the umbrella of OSZMK (host institution of NRDC) and the University of Pecs. This unit operates under the monetary support of the University of Pecs.

The NRDC cooperates with the National Ministerial Board for Clinical Genetics and with the officials responsible for rare diseases policy at the Ministry of Health, and at the National Institute for Quality and Organisational Development in Healthcare and Medicines (GYEMSZI). Project based collaboration has been established with universities' rare disease coordination units, sociological centres (for studying sociological characteristics of the patient groups), the National Centre for Statistics (for studying the mortality trends of rare diseases), and the Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS).

At the Europlan Hungarian national conference on rare diseases²⁵⁰, organised by HUFERDIS on 18-19 October 2010 in Budapest, it was suggested that the issue of rare diseases should be adapted into the present, on-going reorganisation of the health care and social care system.

At the end of 2011, the main content of the plan was finalised and an expert meeting was held to finalise the chapters. Expert opinion was sought on the plan in March 2012. The third Hungarian Europlan

²⁵⁰http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_%20hungary_europlan.pdf

Conference on Rare Diseases²⁵¹ (16-17 November 2012) was organised by HUFERDIS, together with the Ministry of National Resources, in Budapest. All stakeholders were present during the two day conference aimed at defining further concrete steps to develop a national action plan for rare diseases.

By the end of 2012 the plan was submitted to the Ministry of Health. The legal status of the document and budgetary considerations are still to be considered. The national conference, organised by HUFERDIS with the participation of the Ministry of Health examined the document and the budgetary question. It was hoped that the text of the plan will be finalised by the middle of 2013. The plan includes a proposal for the designation of centres of expertise in accordance with the EUCERD Recommendations. In 2012 an expert group was also established at the Ministry of Health to identify the technical specification for a pilot study concerning the introduction of Orphacodes into hospital and healthcare centre records.

Centres of expertise

There are currently no officially approved centres of expertise in Hungary, although around eight are informally recognised. There are four university centres with expertise in the field of rare diseases and diagnostic and therapeutic facilities: Budapest, Szeged, Pecs and Debrecen. In Hungary, a committee on the treatment of rare conditions has been set up within the Scientific Health Council (*Egészségügyi Tudományos Tanács*). It ensures, *inter alia*, that people suffering from such conditions receive adequate care in all cases. People suffering from rare conditions in Hungary are registered at the treatment centres.

Two main factors are to be considered for the designation of Hungarian national centres of expertise: the presence of equipment for diagnosis, and personal expertise of the medical professionals in the centre. In Hungary, the need for 5 rare disease centres playing a coordinating role has been identified. The 4 existing medical universities could play this role, but it has to be assured that the adequate expertise is provided in these centres. Healthcare pathways will be considered as will interdisciplinary, which should be a key feature of the designation. In the National Plan for Rare Diseases, therefore, the strategy will be to designate the four medical universities as centres of expertise due to the existing structure of the health system by speciality and the prominence and reputation of the medical university in terms of research, amongst other disciplines. There are expert groups outside of the medical universities who respect the criteria, but the ways of involving these groups into the existing structures need further examination.

NRDC initiated a collaboration with the National Health Insurance Fund for the listing and transparent accreditation of centres of expertise, hospitals, and laboratories working in the field of rare diseases taking into account existing resources and their concentration, as well as eliminating parallelism and formalising existing informal relations and determining patients' pathways. The research project final report is expected to be published in 2013.

The NRDC has also initiated an open registry concerning the activities of centres of care and expertise, including the activities of consultants and laboratories requiring accreditation.

Registries

The National Register of Congenital Anomalies (VRONY) operates countrywide according to the EUROCAT protocol. The NRDC has initiated the establishment of an overall register for rare diseases. Currently, the clinical centres of rare diseases maintain registries of cared patients: these registries do not report their cases to a national data collecting system, and their registration methodology is developed according to the local need of care management and to the research requirements. All of these registries are in line with the Hungarian laws on genetic data handling and on the personal data protection. Hungary contributes to European Registries such as TREAT-NMD, EUROCAT, SCNIR and EURO CARE CF.

Neonatal screening policy

A compulsory, government-financed newborn screening program covering the whole country has been running since 1975, and after introduction of tandem mass spectrometry screening in 2007, now includes 26 diseases, amongst which phenylketonuria, hypothyroidism, galactosaemia and biotinidase deficiency which belong to the classic core. Two centres are responsible for the operation of this nationwide network.

A HURO-euro programme started in May 2011 on the "Newborn screening and molecular genetic diagnosis of rare diseases: developing a Euro-regional infrastructure and cooperation". The University of Szeged is the project leader, and the Clinic de Urgență pentru Copii "Luis Țurcanu", (Timișoara) and Universitatea de Vest "Vasile Goldis" (Arad) are the Romanian partner institutions. The cooperation was active in 2012.

²⁵¹ <http://europlan.rirosz.hu/>

Genetic testing

The Genetic Professional College established in 2004 a protocol adopted by the Ministry of Healthcare entitled *Genetic Consultation*, which defines the conditions necessary for supplying the laboratory background, the infrastructure and the personal/operational costs for genetic diagnosis. Around 20% of laboratories have at least one diagnostic test validated by an external quality control scheme. The National Centre for Healthcare Audit and Inspection has also initiated an open registry including laboratories requiring accreditation.

Genetic diagnostic testing abroad is available through an application process to the National Health Insurance Fund and in many instances the Fund reimburses the costs.

Diagnostic tests are registered as available in Hungary for 57 genes and an estimated 77 diseases in the Orphanet database²⁵².

National alliances of patient organisations and patient representation

The Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS) is the national alliance of 40 rare disease patient organisations in Hungary, affiliated with EURORDIS. HUFERDIS is currently encouraging the creation of a Hungarian Rehabilitation Centre for Rare Disease Patients which has got into the priority list of Norwegian grant of Hungary. HUFERDIS represents rare diseases patients in the Hungarian Expert Committee of Rare Diseases (which is now the National Plan Organising Committee), the Council of National Alliances (CNA) of EURORDIS, and at the EUCERD.

Patient organisations provide information and act as contact points for rare disease patients and organise conferences. HUFERDIS organised an Expert Committee to help the National Plan Organising Committee in the development of National Plan, and participates in the accreditation of centres of expertise, the determination of guidelines, and in the therapeutic education and care programs, medical and social care training etc.

Non-medical services for rare disease patients are currently available at local level or by non-profit organisations. Patient organisations are partly supported by the '1% Law' which allows taxpayers to transfer 1% of their previous year's taxable income to a non-profit organisation (which may be a patient organisation), without loss of income. Grants from the new National Fund of Cooperation are also available to patient organisations. There is no regular, direct governmental support for rare disease self-help groups, but there are many indirect governmental financing mechanisms: 25% of the civil budget is from governmental sources. HUFERDIS does not receive nominative state support such as that received by other umbrella patient organisations in Hungary.

Following previous collaboration established between HUFERDIS, NRDC and the Hungarian Orphanet team, new projects were not carried out because of the reorganization of NRDC. However a new system was established at the National Health Insurance Fund for the evaluation of high valued medicines and care, and the representatives of HUFERDIS were invited to this expert committee. HUFERDIS takes part in several international projects including Europlan, POLKA, BURQOL-RD, Rare Disease Days, EUPATI, etc. To foster the opinion of patient representatives on future European policies for rare diseases, or to collect their views on existing ones, HUFERDIS participated on the European POLKA project coordinated by EURORDIS. HUFERDIS started new cooperation with other international organizations as well, including DIA, EPF, EPHA, ECOP, ISOQOL.

Sources of information on rare diseases and national help lines

Orphanet activities in Hungary

Since 2004 there is a dedicated Orphanet team in Hungary, initially hosted by the University of Pecs. After its establishment, the NRDC was designated as the official Orphanet team for Hungary in 2010 by the Ministry of Health. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The Orphanet website is widely used by professionals. There is an Orphanet national website launched in 2012, in the Hungarian language²⁵³.

Official information centre for rare diseases

There is currently no official information centre for rare diseases in Hungary apart from Orphanet.

²⁵² Information extracted from the Orphanet database (December 2012): an update has been provided to the coordinating team which is being entered into the database.

²⁵³ <http://www.orpha.net/national/HU-HU/index/honlap/>

Helpline

There is currently no rare disease specific helpline in Hungary. Many patient organisations provide support by telephone.

Other sources of information

Some websites, maintained by the government (www.gyemszi.hu, www.oefi.hu/aboutus.htm), have limited information concerning rare diseases. Scientific societies (www.mhgt.hu), non-governmental expert groups (www.betegmagzat.hu) and market-based organisations (www.webdoki.hu) have web based services for patients. The only other significant rare disease-specific website is the homepage of HUFERDIS (www.rirosz.hu). Several member associations of HUFERDIS have also detailed specific websites for a given rare disease.

Good practice guidelines

Guidelines related to rare diseases have been produced by the Ministry of Health and are available including: autism spectrum, cystic fibrosis, diagnosis of the inherited metabolic diseases, genetic counselling, haemophilia, investigation of familial clustering of anomalies, investigation of multiple congenital anomalies, Legg-Calve-Perthes disease (Perthes disease), multiple sclerosis, myasthenia gravis, Osgood-Schlatter disease, prenatal screening of Down syndrome, Scheuermann disease, systemic lupus erythematosus, Tibial hemimelia, clubfoot. Hungary supports the participation of local experts in the development of international guidelines that should help diagnosis and care of rare diseases patients at national level. Some guidelines have been developed in collaboration with patient organisations and specialised clinics, in line with the new European guidelines (e.g. Williams syndrome). One of the missing guidelines in the field of rare diseases was a national protocol for the communication of a diagnosis: another expert team of HUFERDIS has thus developed a new rare disease protocol to properly communicate a diagnosis.

Training and education initiatives

The education provided to health professionals currently includes information about the existence of rare diseases and the resources available for their care. This includes medical training in fields relevant to the diagnosis of rare diseases (genetics, oncology, immunology, neurology, paediatrics), further education for young doctors and scientists working in the field of rare diseases, and exchange and sharing of expertise between centres of expertise in the country.

Annual courses on rare diseases for graduates and postgraduates have been held at the Debrecen University, Department of Rare Diseases, since 2003 (with 40-100 participants). Rare diseases are also discussed at the Days of Internal Medicine of Debrecen (100-150 participants) which have been held seven times to date. The Department of Medical Genetics at the University of Pécs has organised since 2009 3-day clinical genetics course covering among others the diagnosis and management of selected rare diseases; the meeting is intended for specialists in the field as well as for family practitioners. The course in October 2012 aimed to show the interdisciplinary participation of various disciplines in the diagnosis and care of rare disease patients. The institutions and clinics participating in rare disease care constitute a Rare Disease Network of the University of Pécs established in February 2012. The Hungarian Clinical Neurogenetic Society organises annual meetings, which focuses on inherited neurological and neuromuscular disorders. The Semmelweis University also organises courses even for patients such as the “Molecular Medicine for Everybody”. Regular conferences are organised on the area of rare diseases by the Hungarian Society of Personalised Medicine or by Industry, like the Personalised Healthcare Days of Roche.

The Epidemiology of Rare Diseases has been accepted as research area by the Health Sciences Doctoral School of University of Debrecen. The students are involved in the folic acid supplementation, prenatal screening, patient pathway and diagnostic delay investigations.

National rare disease events in 2012

HUFERDIS, the Hungarian rare disease alliance, organised a number of events to mark Rare Disease Day in Hungary on 25 February 2012 in Budapest. As usual, many parallel programmes was arranged: expert conference, poster section, games and handcrafting for children, entertainment programmes, “Rare Beauties” Art Exhibition, concerts, press conference, all-day exhibition of the HUFERDIS member associations. Many videos and report are available²⁵⁴). The main breakthrough of the programme was the section dealing with

²⁵⁴<http://ritkanap.rirosz.hu/eddigi-ritka-napok/ritka-nap-2012/videok-interjuk-2012>

social problems of rare diseases for the first time: four leaders of the Ministry of Social Affairs participated and gave talks²⁵⁵.

For the second time, Rare Disease Day in Hungary was organised in two cities simultaneously. In addition to the events in the capital, Budapest, events were also held in the university town of Pécs, in southwest Hungary. The initiative to organise Rare Disease Day events at multiple locations allows Hungarian rare disease patients to participate in the events nearer to their hometowns. As a joint effort of the Department of Medical Genetics of the University of Pécs, the Életes Mátyás School for Children with Special Needs, and the Pécs Gallery at the Zsolnay Cultural Center, an information day for all rare disease patients in the region was held on 23 February, 2013. The backbone of the program consisted of musical performances by the students of the Életes Mátyás School, many of whom are affected by rare diseases themselves, and information stands of various Hungarian rare disease patient organizations and caregivers from the region. The guest of honour at this year's scientific program was Daria Julkowska, program coordinator of E-Rare2, the ERA-Net on Rare Disease Research Funding. Hungary joined the E-Rare2 network in 2010, and was able to participate through contributions from the University of Pécs, and the Hungarian National Research Fund. Daria Julkowska gave both a broad overview on E-Rare2 activities and achievements, as well a model of rare disease national coordination, using the example of the French Rare Disease Foundation. The broad interest in rare diseases, and the success of the local events strengthened the organizers in their ambition to continue this tradition, and even inspire other regions in Hungary to organise local events on future Rare Disease Days.

The third Hungarian Europlan Conference on Rare Diseases²⁵⁶ (16-17 November 2012) was organised by HUFERDIS, together with the Ministry of National Resources, in Budapest. All stakeholders were present during the two day conference aimed at defining further concrete steps to develop a national action plan for rare diseases

Hosted rare disease events in 2012

Amongst the events hosted by Hungary and announced in *OrphaNews Europe* was the 8th International Society for Newborn Screening European Regional Meeting (4-6 November 2012, Budapest).

Research activities and E-Rare partnership

National research activities

Governmental research funds for rare diseases are available from the Hungarian Scientific Research Fund. The Ministry of Health announces its health related research grants through the Scientific Health Council (ETT), Department of Research Coordination every three years. In the last evaluated period (2009-2011) 166 research grants were supported from 495 applications²⁵⁷. In these programs, rare diseases were not one of the priority areas, but many rare diseases related grants were financed (e.g. governmental supported the project on the periconceptional folate status and on attitude towards different supplementation programs).

A multidisciplinary centre had been established in the Semmelweis University (Budapest) on rare disorders. The centre organises its work according to the principals published in the Communication from the European Commission on Rare Diseases. The centre has a patient registry, a diagnostic department, a multidisciplinary care providing network, research projects, and a teaching program²⁵⁸. The coordinator of this Rare Disease Centrum is the Institute of Genomic Medicine and Rare Disorders²⁵⁹.

To ensure the scientific expertise for NRDC, the general director of the National Centre for Healthcare Audit and Improvement, the rector of Pecs University, and the head of the Department of Medical Genetics signed the detailed agreement which established the National Rare Disease Research Coordinating Centre on the 21 April 2009; this Centre is still embedded into the Department of Medical Genetics of University of Pecs. The Medical Faculty, Faculty of Health Sciences and the Faculty of Special Pedagogy are involved in this cooperative project. The experts employed by these faculties come from the fields of medicine, paramedicine, social services and education. This working environment is expected to improve the Hungarian teams' ability to contribute to the work of European organisations.

All Hungarian Medical Faculties have started to establish their own coordinating centres to harmonise their rare diseases related activities, including research.

²⁵⁵ In addition, some videos were released by Bach Rezsőó Bach: <http://youtu.be/JKiGdF-fvHg>, and Gábor Pogány: <http://youtu.be/Z-i8R - CzU4> Hungary (Society of Aiders and People suffering from Neurofibromatosis).

²⁵⁶ <http://europlan.rirosz.hu/>

²⁵⁷ The summary report of the 2009-2011 program evaluation is available here: http://www.ett.hu/palyazat/tam_09_11.pdf

²⁵⁸ <http://www.molneur.eoldal.hu/cikkek/english>

²⁵⁹ <http://semmelweis-egyetem.hu/genomikai-medicina/>

The IT centre of the NRDC elaborated the on-line registration system for health care providers, laboratories, research programs and patient groups related to rare diseases. This data collection is in line with the Orphanet data collection standards. The system has been launched and the primary database is used to contribute to the Orphanet database.

Participation in European research projects

Hungary participates, or has participated, in European rare disease research projects including: BNE, EURO BONET, EURO GENTEST, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, NMD-CHIP, TREAT-NMD, SCRIN-SILICO, OPTATIO, BBMRI and SIOPEN-R-NET.

E-Rare

Hungary is full partner of E-Rare-2 via the National Rare Disease Research Coordinating Centre at University of Pécs. Hungary did not participate in the 4th Joint Transnational Call in 2012.

IRDiRC

Hungarian funding agencies have not currently committed funding to the IRDiRC, but as part of the E-Rare group of funders there is the possibility for Hungary to participate in the IRDiRC through the University of Pecs.

Orphan medicinal products²⁶⁰

The holders of marketing authorisations for orphan medicinal products (or their representatives in Hungary) cooperate with the medical profession and the OEP (The National Health Insurance Fund - *Országos Egészségbiztosítási Pénztár*).

Orphan medicinal product committee

There is no committee for orphan medicinal products in Hungary, but there is a new committee for the evaluation of reimbursement inclusion decisions in case of highly expensive medicines and care. A new system was established at the National Health Insurance Fund for the evaluation of high valued medicines and care, besides professionals caring for patients with rare diseases where high valued therapy is available, the representatives of HUFERDIS were invited to this expert committee. The committee has issued guidelines on the diagnosis, treatment and care of various rare diseases where therapy is available, those guidelines serve as a basis for the individual decision on the reimbursement of high valued orphan drugs to Hungarian rare disease patients.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

At the beginning of 2011 in Hungary, 69 of the 74 orphan medicinal products were available according to the Department of Rare Diseases in University of Debrecen. This institution implemented in Hungary the survey of the Rare Disease National Alliances & EURORDIS on Patients' Access to Orphan Medicinal Products in Europe. Most of orphan medicinal products are available via centres assigned by the National Health Insurance Fund.

The orphan medicinal products on the market in Hungary are: Afinitor™ (Everolimus), Aldurazyme™ (Laronidase), Arzerra™ (Ofatumumab), Atriance™ (Nelarabine), Busilvex™ (Busulfan (Intravenous use)), Carbaglu™ (N-carbamyl-L-glutamic acid), Cayston™ (Aztreonam lysinate inhalation use), Ceplene (Histamine dihydrochloride), Cystadane™ (Betaine anhydrous), Diacomit™ (Stiripentol), Dudopa™ (Levodopa/Carbidopa gastrointestinal use), Elaprased™ (Iduronate-2-sulfatase) , Evoltra™ (Clofarabine), Exjade™ (Deferasirox), Fabrazyme™ (α-Galactosidase A), Firazyr™ (Icatibant acetate), Firdapse™ (Amifampridine), Gliolan™ (INN-5-aminolevulinic acid hydrochloride), Glivec™ (Imatinib mesilate), Ilaris™, Increlex™ (Mecasermin rinfabate), Inovelon™ (Rufinamid), Ixiaro™, Kuvan™ (Sapropterin dihydrochloride), Litak™ (Cladribine), Lysodren™ (Mitotane) , Mepact™ (Muramil Tripeptid Foszfátidil Etanolamin), Mozobil™ (Plerixafor), Myozyme™ (Recombinant human acid α-glucosidase), Naglazyme™ (N-acetyl galactosamine 4-sulfatase), Nexavar™ (Sorafenib tosylate), Nexavar™ (Sorafenib tosylate) , Nplate™, Nymusa™ (Caffeine citrate), Onsenal™ (Celecoxib) , Orfadin™ (Nitisinone), Pedeas™ (Ibuprofen), Photobarr™ (Porfimerum for photodynamic therapy), Prialt™ (α-Galactosidase A), Replagal™ (α-Galactosidase A), Revatio™ (Sildenafil citrate), Revlimid™

²⁶⁰ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

(Lenalidomid), Revolade™ (Eltrombopag olamin), Savene™ (Dexrazoxane), Siklos™ (Hydroxyurea), Soliris™ (Eculizumab), Somavert™ (Pegvisomant), Sprycel™ (Dasatinib), Tassigna™ (Nilotinib), Tassigna™ (Nilotinib), Tepadina™ (Thiotepa), Thalidomide Celgene™ (Thalidomide), Thelin™ (Sitaxentan), Torisel™ (Temsirolimus), Tracleer™ (Bosentan), Trisenox™ (Arsenic trioxide), Ventavis™ (Iloprost), Vidaza™ (Azacitidin) , Vidaza™ (Azacitidine), Volibris™ (Ambrisentan), Votrient (Patorma)™ (Pazopanib hydrochloride), Wilzin™ (Zinc acetate dihydrate), Xagrid™ (Anagrelide Hydrochloride), Yondelis™ (Ecteinascidin 743), Yondelis™ (Trabectedin), Zavesca™ (Miglustate).

Orphan medicinal product pricing policy

The OEP does not have a direct impact on pricing.

Orphan medicinal product reimbursement policy

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal product*²⁶¹, “the Hungarian Government promotes the use of orphan medicinal products for specific patients by means of special financial arrangements”.

“Some rare conditions (such as Fabry disease or adult-type chronic myeloid leukaemia - CML), the National Health Insurance Fund (OEP) provides standard price-support for the medicinal products in a predetermined manner. In this case the patient's contribution is negligible or 0%. In other cases, support for the orphan medicinal products imported for patients' treatment can be provided on application under a special equity procedure laid down by law. The OEP pays the price-support for the necessary medicinal products from earmarked resources in the outpatients' equity fund”²⁶². In most cases, support is only available via discretionary claims. There is a yearly budget for such claims managed by the OEP. The discretionary procedure takes into account the financial situation of the claimant. In 2009, 289 patients had their discretionary claims accepted. Around 13 rare diseases receive support within the framework of discretionary claims. 33 orphan medicinal products are 100% reimbursed in Hungary. The re-regulation of pharmaceutical reimbursement inclusion decisions started in 2011. The National Health Insurance Fund established an advisory group to evaluate the applications for expensive medical treatments. The operation rules for this committee have been elaborated. A significant proportion of applications are submitted by rare disease patients' physicians.

Other initiatives to improve access to orphan medicinal products

Off-label use is possible, provided that the benefits of the drugs for a certain disease are certified, but the process is highly bureaucratic.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

No specific activity reported

Specialised social services

There are good and high quality programs in the field of early development and respite care which support patients and their families. However, these programmes do not cover the whole country. Legislation exists on care, training, integration, work help for special needs children (i.e. extra home care), however these initiatives are not available to all rare disease patients. The change of this legislation has started in favour of rare disease patients. There are measures in place to support patients who need to travel inland to access health care through an assessment of needs by the Health Insurance Fund.

The Ministry of Human Resources started to work together with HUFERDIS for a project establishing the National Habilitation, Development and Service Centre of Rare Disorders to help the social integration of rare disease patients. Several health care institutions started to change care profile during the reorganisation within the Semmelweis Plan. Some of them will be able to offer more rehabilitation and social care.

HUFERDIS joined the therapeutic recreational programs of a member association (Hungarian Williams Syndrome Association) and organised programmes for capacity building and training, networking, awareness

²⁶¹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

²⁶² Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

raising, exchange of information and best practices, during a special development family camp and after. HUFERDIS is also participating in the EUCERD Joint Action activities concerning Specialised Social Services.

1.13. IRELAND

Definition of a rare disease

Stakeholders in Ireland accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

On 20 January 2011 the Genetic and Rare Disorders Organisation, Irish Platform for Patients' Organisations, Science and Industry IPPOSI and Medical Research Charities Group, MRCG in collaboration with EURORDIS organised a National Conference on Rare Diseases²⁶³ in the scope of the Europlan project (see section "National rare disease events"). The conference welcomed over 160 participants from all stakeholder groups. The Conference was "an important milestone" in the development of a national health strategy for rare disease patients.

There is currently no national plan/strategy for rare diseases in Ireland, but the development of a plan is underway. A National Steering Group of stakeholders has been established (Spring 2011) under the aegis of the Department of Health and Children to work on the development of a five-year national plan, starting with a mapping exercise and focusing on the structure, governance and monitoring of a national strategy. The Minister for Health appointed four patient representatives from GRDO, IPPOSI and MRCG to the Steering Group: the Steering Group held their first meeting in April 2011 and meets every 1-2 months with the aim of completing the first plan by the end of 2013.

A national consultation²⁶⁴ was carried out in 2012 on the proposed plan. The Health Service Executive National Advocacy Unit is supporting the Department of Health in its initiative to develop a national rare disease plan. The patient-centred policy framework will encompass actions targeting the prevention, detection and treatment of rare diseases based on the principles of quality care and equity. The policy will operate over a five-year period and define priority actions, subject to resource availability, in the areas of centres of expertise, orphan drugs and technologies, research and information and patient empowerment and support. The National Steering Group invited stakeholders to participate in a consultation process designed to gather views concerning the plan's various components. A National Consultation Day event was held on 11 June 2012. This was followed by an online consultation process which received almost 500 valid responses. The Institute of Public Health, which is providing support for the development of the Plan, is preparing a report on both aspects of the consultation process which it is intended to publish alongside the Plan itself in 2013.

On 7 March 2012 a motion²⁶⁵ was heard in the Seanad Eireann (Senate) on the subject of rare diseases: the Minister for Health, Dr. James Reilly, announced the intention of the Health Service Executive to develop a Clinical Care Programme for Rare Diseases. The recruitment process for a Clinical Lead in Rare Diseases in the Health Service Executive commenced in late 2012.

Centres of expertise

Currently the Department (Ministry) of Health has no specific list of national centres of expertise nor does it set standards for centres to be considered "national". However the Department does recognise that particular centres have particular expertise and would give specific funds to support those specialist services. The Health Service Executive (HSE) is responsible for these services and supports centres of expertise and laboratories, including 8 cancer centres; the National Centre for Medical Genetics at Crumlin Children's Hospital which provides a service for patients (both adults and children) affected by or at risk of a genetic disorder; the National Centre for Inherited Metabolic Disorders, a tertiary care referral centre for the investigation and treatment of patients suspected of having a metabolic genetic diseases, linked to the newborn screening programme; and the National Centre for Hereditary Coagulation Disorders at St. James' hospital which is a

²⁶³ <http://www.europlan.ie/> and

http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_ireland.pdf

²⁶⁴ <http://www.dohc.ie/press/releases/2012/20120614d.html>

²⁶⁵ <http://debates.oireachtas.ie/seanad/2012/03/07/00008.asp>

centre of expertise for rare blood disorders, principally haemophilia. There are also 15 centres for the management of Cystic Fibrosis in Ireland – both paediatric and adult centres (Ireland has the highest incidence of CF in the world). Patients with a rare disease are generally directed towards one of the major children or adult hospitals in Ireland, but for many rare diseases there is not a dedicated multi-disciplinary team to treat such diseases. Some people with a rare disease are directed for shared care to hospitals in the UK.

A policy concerning centres of expertise is under development as part of the national plan for rare diseases.

Registries

There is no designation process for rare disease registries currently in Ireland. There is no national committee or policy statement in relation to any patient registry in Ireland with the exception of the Cancer Registry which is established by Statute. Patient groups, in particular the Medical Research Charities Group (MRCG) and IPPOSI, have called for the establishment of a coordinating body and plan for all patient registries in Ireland, including those with a rare disease. Governance issues in relation to patient registries are being included in a forthcoming Health Information Bill. However financial support or planning for registries will not be included in the legislation.

The Cancer Registry is funded by government. Some registries received some support from Government and others did not. The MRCG will be publishing an overview of the issues facing patient registries in Ireland.

The Medical Research Charities Group (MRCG) created a Steering Group in 2008 involving the MRCG, Health Services Executive (HSE), Health Research Board (HRB) and the Health, Information and Quality Authority (HIQA) to oversee research into the area of patient registries in Ireland. The aim was to identify existing patient registries in Ireland, to describe these in detail (functions, methodologies, standards, funding mechanisms) and also to identify best practice and guidelines for quality standards in this area. The research was presented at an IPPOSI/MRCG run event in October 2011. The outcome report from that event entitled "Towards a National Strategy for Patient Registries in Ireland, considerations for Government"²⁶⁶ was launched in 2011. Part of a national strategy on Patient Registries in Ireland is the mainstreaming of the role and work of registries into existing and forthcoming policy. The immediate priority is the inclusion of a stronger focus on Patient Registries in: the programme of work of the Quality and Clinical Care Directorate of the HSE, including the development of clinical standards in specific areas of policy and the appointment of clinical leads in particular areas of policy; the work of the Health Information and Quality Authority; and the Health Information Bill. The Health Information Bill is expected to be published in 2013 and will address ethical and legal issues concerning data collection and sharing patient data.

There are 11 patient registries for rare diseases registered with Orphanet: 5 of these contribute to the EUROCAT registry. Ireland also contributes to other European registries, such as EUROCAT CF and SCNIR.

Neonatal screening policy

Neonatal screening is in place for galactosaemia, hypothyroidism, phenylketonuria, homocystinuria, maple syrup urine disease and cystic fibrosis²⁶⁷. Concomitant with the addition of CF, the entire governance of the newborn screening programme was reviewed and revised in 2011. The revised programme included the launch of an enhanced information process for all parents and guardians and the introduction of signed consent on individual blood-spot cards.

All cards from 1984 onwards have been archived, but the Office of the Data Protection Commissioner, following a complaint in 2009, indicated that newborn screening cards currently stored without explicit consent should be disposed. The Minister for Health requested the HSE to conduct a review of the decision to destroy these cards following receipt of representations from a number of people and organisations, who pointed out their potential value for research. The review examined both the legal and ethical basis for retention of newborn screening cards and the potential use of the existing cards for research purposes. The report and recommendations of the review group were submitted in January 2012. The review re-affirmed the original decision reached in 2010, i.e. that in order to meet both ethical and legal obligations, newborn screening cards older than ten years should be destroyed. Following careful consideration this recommendation was accepted. The Review Group also explored how the cards could be made available to the research community in a way which is compatible with ethical and legal obligations. In the interests of facilitating research, the HSE launched a public information campaign on 8 January 2013. This campaign offering members of the public the

²⁶⁶ <http://ipposi.ie/index.php/information-centre/patient-registries/179-towards-a-national-strategy-for-patients-registries-report>

²⁶⁷ <http://www.hse.ie/eng/services/healthpromotion/newbornscreening/>

opportunity to have their screening card returned to them, prior to any destruction of the cards taking place, ended on 31 March 2013. The HSE has received approximately 40,000 requests from people seeking to have cards returned to them.

The Minister has sought advices from the Attorney General on how the remaining New born Screening Cards can be retained in compliance with Irish and EU data protection legislation. The Minister has also requested that no destruction of the cards begins before an expert group has had an opportunity to consider the matter further.

Genetic testing

Genetic testing in the Republic of Ireland is available through the National Centre for Medical Genetics (NCMG)²⁶⁸, Our Lady's Children's Hospital, Crumlin, which processes approximately 13,000 cytogenetic and molecular genetic tests annually. The cytogenetic and molecular genetics laboratories are externally accredited by CPA (UK). The National Centre for Medical Genetics is publicly funded via the Irish Health Service Executive. When a genetic test is not available from a laboratory in Ireland, and is clinically indicated, DNA samples are sent to specialised laboratories abroad.

Diagnostic tests are registered as available in Ireland for 23 genes and an estimated 47 diseases in the Orphanet database²⁶⁹.

The Disability Act Part IV, passed by the Oireachtas and signed into law in 2005 states that genetic testing shall not be carried out unless the consent of the person has been obtained. In addition, genetic tests cannot be used in relation to employment, insurance, pensions or mortgages.

A small amount of genetic testing is also available in private clinics.

National alliances of patient organisations and patient representation

The Rare Disease Taskforce

The Rare Diseases Towards 2013 Taskforce was set up in 2011 by the Medical Research Charities Group (MRCG), the Genetic and Rare Disorders Organisation (GRDO) and the Irish Platform for Patients' Organisations, Science and Industry (IPPOSI). The Taskforce brings the three umbrella organisations together to work collaboratively to ensure that the needs of the Rare Diseases stakeholders are represented in the National Strategy for Rare Disease 2013.

The Minister for Health has established a National Steering Group which is tasked with developing a five year national plan and which will deal with the diagnosis, prevention, management, treatment and research of rare diseases in Ireland. The Rare Disease Taskforce will support this National Steering group and provide input from the appropriate stakeholders. The aim of the 2013 Taskforce is the delivery by the State of a comprehensive, targeted and achievable National Strategy for Rare Diseases by 2013.

GRDO, MRCG & IPPOSI as part of the Rare Disease Taskforce came together in 2012 to plan and organise Rare Disease Day on 28th of February 2013 with the theme of Rare Disorders without Borders which addressed the EU directive on cross border healthcare for Ireland. In keeping with the theme of cross border co-operation this event was organised along with the Northern Ireland Rare Disease Partnership (NIRDPA) and Rare Disease UK. IPPOSI took the lead in co-ordinating and organising this event.

Genetic and Rare Diseases Organisation (GRDO)

The Genetic and Rare Disorders Organisation (GRDO) is a non-governmental organisation created in 1988 which acts as an umbrella group for rare disease patient organisations. GRDO was initially founded with a view to lobbying for the establishment a National Centre for Medical Genetics. In 1992 this Centre was established by Government. Until October 2011, the organisation was run by volunteers and has since 1988 acted as an advocate for the voluntary sector concerned with genetics. This has been achieved by creating awareness and providing information on genetic disorders to policy makers and health officials in order to achieve a high quality of services for those directly affected by genetic conditions and their families. GRDO also acts as a watchdog in relation to legislation concerning disability to ensure that the rights of people with genetic conditions are protected: the organisation was involved in the consultation process for the Disability Act, 2005 resulting in the inclusion in the Act of provisions regarding genetic tests. Since October 2011, a part-time employee has been hired by GRDO to facilitate the development of the organisation.

At the end of 2011 GRDO launched a survey to gather information relating to patient support and advocacy organisations operating in Ireland for people with rare conditions. This information is being used to

²⁶⁸ <http://www.genetics.ie/>

²⁶⁹ Information extracted from the Orphanet database (December 2012).

assist the Taskforce to engage with the Rare Diseases Steering Committee of the Department of Health. The results of this survey were published on Rare Disease Day 2012, which highlighted the urgent need for development of co-ordinated healthcare pathways and a central information point on rare conditions.

The results also reveal significant difficulties in the areas of access to diagnosis, information and to treatment, as well as a lack of coordination in delivery of services. 13.3% of respondents report waiting more than 10 years for diagnosis and 37.2% report receiving an incorrect diagnosis before the correct one. 73.1% of those surveyed report attending more than one hospital consultant or other medical professional for treatment yet 44.8% report not having a specific point of contact to go to with questions about their condition. 62.5% of respondents list the Internet as their main source of information. The establishment of a National Rare Disease Office in Ireland and the development of co-ordinated healthcare pathways are the two changes to the healthcare system that respondents would most like to see (82%), followed by more information about their conditions (73%). A national office would act as a focal point for the development of a national registry of rare conditions, and a vitally needed information portal for patients and medical professionals. It would help patients to access Centres of Expertise, whether in Ireland or abroad, and ensure the best model of care for patients with faster diagnosis and access to treatment. It would also be cost efficient.

In the context of developing a National Rare Disease Plan and the EU Directive on the Application of Patients' Rights in Cross-border Healthcare, GRDO is working to establish a cross border working group with the equivalent organisation in Northern Ireland, the Northern Ireland Rare Disease Partnership.

The Irish Platform for Patients' Organisations, Science and Industry (IPPOSI)

IPPOSI has a special interest in the rare disease area given that one of its strategic objectives is to address together with key stakeholders (patients' organisations, scientists and industry (and where possible with State Agencies) policy, legislation and regulation around the development of new medicines, products, devices and diagnostics for unmet medical needs. As a non-lobbying organisation, a unique partnership of patient groups/medical charities, science and industry, IPPOSI works to smooth the path in Ireland for new medicines and therapies to move from basic science in laboratories to the patients who need them. This is achieved through expertise, dialogue, consensus building, networking etc. Since its establishment in 2001 the organisation has been involved in a number of conferences relating directly and indirectly to the rare disease area and to therapy development for unmet medical need including Orphan Medicinal Products Regulation of the EU; the Commercialisation of Health Research, the EU Clinical Trials Directive, Clinical Research Infrastructure in Ireland, Access to Medicines and New Medical Technologies in the Era of Health Technology Assessments in Ireland, Patient Registries in Ireland etc. IPPOSI have a place on the Ministry for Health Steering Group developing a strategy for Rare Diseases in Ireland and are members of the National Rare Disease Taskforce.

The Medical Research Charities Group (MRCG)

MRCG was formed in 1998 to inform and support charities in Ireland in the development of their medical research. As an alliance promoting medical research, the MRCG works to raise the profile of medical research, increase funding, and ultimately alleviate suffering and mortality caused by illness. Since 2006 the MRCG charities have been co-funding research projects with the Health Research Board (HRB). This is made possible by an allocation of funding to the HRB from the Department of Health and Children. While the scheme does not focus solely on rare diseases a number of research projects in the area have been funded. Since the Scheme was put into action in 2006, 44 projects (covering rare and non-rare conditions/diseases) have been supported. In this joint funding scheme the Department of Health and Children provides an on-going annual allocation of €1 million to the HRB which is matched by the research charities. Total investment for the three years 2006, 2007, 2008 was €6 million of which €3 million was provided by the Department of Health.

In addition to the joint funding scheme activities, the MRCG also has a working group on rare diseases and has prepared a policy paper on rare diseases entitled "It's not rare to have a rare disease".

Sources of information on rare diseases and national help lines

Orphanet activities in Ireland

There has been an Orphanet national coordinator based in Ireland since 2004. However, the funding for an operational team finished in March 2011. Since then the Orphanet UK team, hosted by the University of Manchester in the UK, has been taking care of the Orphanet Ireland activities on a voluntary basis. The main activities are data collection and validation. This team is in charge of collecting data on rare disease related services (expert centres, specialised clinics, medical laboratories, ongoing research, registries and databases, clinical trials, networks of excellence and patient organisations), the annual update of information, regular data

quality controls, the point of contact of Orphanet Ireland and the management of the national Irish website²⁷⁰, launched in April 2011. It is the intention that the National Plan currently being developed will recommend that the running of the Orphanet for Ireland will be relocated to Ireland.

Official information centre for rare diseases

There is no official information centre for rare diseases in Ireland other than Orphanet. However, GRDO operates as a conduit to information on rare diseases and it is hoped that the National Plan for Rare Diseases currently in development will prioritise the establishment of a national information centre for rare diseases.

Help line

There is currently no help line dedicated to rare diseases in general, but some disease specific help lines exist and are funded through public/private partnerships.

Other information on rare diseases

Patient groups are currently providing a significant level of information on particular diseases. However where a rare disease does not have a patient group, the level of information can be minimal/very patchy. The Rare Disease Task Force (GRDO/IPPOSI/MRCG) has highlighted the need for more comprehensive information on rare diseases to be provided by Government under the national plan.

Public information about rare diseases is also provided by patient organisations and GRDO. The MRCG supports patient groups and charitable organisations in securing research funding for rare diseases. Irish Platform for Patients' Organisations, Science and Industry (IPPOSI)-provides web-based information and policy support to patient groups. IPPOSI and MRCG are funded partly by the government and membership fees.

In 2008 a report entitled *An investigation into the social support needs of families who experience rare disorders on the island of Ireland* published by Rehab Care, a unit of the independent non-profit organisation Rehab Group²⁷¹ and funded by Ireland's Health Research Board discovered an urgent need for information and support resources for both patients and medical professionals encountering rare disease patients in their practice. The report recommended developing a centre of excellence in Ireland dedicated to rare diseases that could support health professionals and also provide materials suitable for patients and their families. The authors recommend that Orphanet, as a freely-accessible information resource for professionals and patients, receive a high profile in Ireland, along with UK charity Contact a Family²⁷².

Good practice guidelines

Clinical guidelines exist for certain rare diseases. The need for an overall Clinical Programme for Rare diseases has been accepted by the Minister for Health and recruitment is underway for a National Clinical Lead in Rare Diseases in the Health Service Executive. It is anticipated that one of the roles of the person appointed to this position will be to instigate the development of clinical guidelines.

Training and education initiatives

In 2011 IPPOSI and the School of Medicine and Medical Sciences (SMMS) at University College Dublin launched a Rare Disease Module for 3rd year medical students. IPPOSI/UCD planned the first module of its kind in Ireland to focus exclusively on rare diseases and the impact on patients. The module is entitled Rare Genetic Disorders and the Medical Healthcare Professional. The lecturers on this module are scientists, clinicians and patients describing their own condition to students. The plan is to role this out to other medical schools in Ireland and Europe to bring patients and their patient organisations into the classroom.

National rare disease events in 2012

To mark Rare Disease Day 2012 in Ireland GRDO planned a number of initiatives. The GRDO addressed the Joint Oireachtas Committee^{273&274} on 29 February 2012, which was aimed at providing committee members with an in-depth briefing on the issue in Ireland and providing the groups dealing with various rare diseases with an opportunity to outline the key issues they face in terms of prevention, detection and treatment of rare

²⁷⁰ www.orphanet.ie

²⁷¹ <http://www.rehab.ie/index.aspx>

²⁷² <http://www.cafamily.org.uk/index.php?section=861>

²⁷³ <http://media.heanet.ie/oireachtas/asx.php?Channel=Committee1&Date=20120229&StartTime=05%3A00%3A00.000&Duration=02%3A00%3A00.000>

²⁷⁴ <http://www.oireachtas.ie/parliament/mediazone/pressreleases/name-6924-en.html>

diseases, access to appropriate medication and the identification of appropriate centres of expertise for rare diseases which is a key priority.

The results of the GRDO-led patient survey on the experiences of people in Ireland with rare conditions were published on Rare Disease Day 2012. The survey highlights the urgent need for development of co-ordinated healthcare pathways and a central information point on rare conditions. The information from the survey will be used by GRDO, together with the Medical Research Charities Group (MRCG) and the Irish Platform for Patients' Organisations, Science and Industry (IPPOSI) and their patient representatives to assist the National Rare Diseases Taskforce ('Towards 2013 - the National Plan for Rare Diseases') to engage with the Rare Diseases Steering Committee of the Irish Government's Department of Health.

In addition, GRDO launched a postcard campaign to highlight Rare Disease Day in Ireland, including images from the official Rare Disease Day video which was filmed in Dublin : the postcards were delivered to politicians and other public figures, as well as to media representatives across Ireland. In addition, GRDO produced a new Easy Guide public information booklet on rare disease in Ireland which was launched on Rare Disease Day 2012.- This was accompanied by an awareness-raising campaign.

On 11 June 2012, the Department of Health's Consultation Day on the National Rare Disease Plan took place in Dublin. An online consultation process was also launched, offering all those affected the opportunity to contribute to the formation of the plan.

On 26 March 2012 a workshop hosted by the Health Research Board on behalf of the National Steering Group for Rare Diseases was held to provide an opportunity for stakeholders to input to planning for the future of rare disease research in Ireland and inform deliberations in the area of research for the forthcoming Irish National Plan for Rare Diseases.

IPPOSI, the Irish Platform for Patients' Organisations, Science and Industry holds 2-3 conferences annually to tackle various questions in the field of rare diseases and orphan medicinal products: in June 2012 a roundtable on access to new therapies and treatments²⁷⁵ was organised.

In June 2012, IPPOSI facilitated a roundtable discussion with its members and invited guests, on the issue of Access to Innovation which was an issue for Rare Diseases and other diseases. The Board of IPPOSI decided to call this meeting in response to reports of treatments which had been approved for reimbursement but were not reaching patients. IPPOSI asked key patient organisations to outline the issues and clarify the situation for their patient members. Key contributions were made by the Irish Cancer Society, MS Ireland and Fighting Blindness. IPPOSI also launched the Outcome Report on their website on 11 October 2012, IPPOSI members welcomed the presence of the Secretary General of the Department of Health at the roundtable and IPPOSI has subsequently met with the Secretary General to discuss the issue further. An announcement was made by the Department of Health on 18 June 2012 which saw the Health Service Executive (HSE) give approval to the reimbursement of certain treatments.

On 17 September IPPOSI hosted an event where a well known Broadcaster and the CEO of the Health Research Board, launched a new information campaign aimed at people who have been asked to participate in a clinical trial. The clinical research information campaign includes a new leaflet and dedicated website which will provide patients with independent answers to many of the questions which they may have about clinical trials.

IPPOSI held an information day on the process of Health Technology Assessments (HTA) in Ireland on 11 October 2012. IPPOSI members attending represented key individuals from leading patient organisations, clinicians, researchers and industry. The aim of the event was to explain how pharmaceutical products are assessed to further inform pricing and reimbursement decisions made by the HSE and/or the Department of Health. Patient organisations articulated a willingness to get involved in the HTA process at the earliest stage. The Director of the Irish National Centre for Pharmaco-Economics (NCPE) agreed that this was an area the NCPE are interested in pursuing and indicated that IPPOSI would be an ideal partner in linking his team with relevant patient groups as new applications arrive in to the NCPE office.

Hosted rare disease events in 2012

No specific reported information.

Research activities and E-Rare partnership

National research activities

²⁷⁵<http://www.ipposi.ie/index.php/news-a-events-mainmenu-28/227-outcome-report-from-ipposi-roundtable-on-access-to-new-treatments-and-therapies->

The Medical Research Charities Group (MRCG) was formed in 1998 to inform and support charities in Ireland in the development of their medical research. As an alliance promoting medical research, the MRCG works to raise the profile of medical research, increase funding, and ultimately alleviate suffering and mortality caused by illness. Since 2006 the MRCG charities have been co-funding research projects with the Health Research Board (HRB). This is made possible by an allocation to the HRB from the Department of Health and Children. While the scheme does not focus solely on rare diseases a number of research projects in the area have been funded. Since the Scheme was put into action in 2006, over 40 projects (covering rare and non rare conditions/diseases) have been supported. In this joint funding scheme the Department of Health and Children provides an ongoing annual allocation of €1 million to the HRB which is matched by the research charities. Total investment for the three years 2006, 2007, 2008 was €6 million of which €3 million was provided by the Department of Health.

In addition to the joint funding scheme activities, the MRCG also has a working group on rare diseases and has prepared a policy paper on rare diseases entitled "It's not rare to have a rare disease"²⁷⁶.

On 26 March 2012 a workshop hosted by the Health Research Board on behalf of the National Steering Group for Rare Diseases, brought together national and international speakers and Irish researchers. This meeting was intended to provide an opportunity to input to planning for the future of rare disease research in Ireland and inform deliberations in the area of research for the forthcoming Irish National Plan for Rare Diseases. This event outlined how Ireland can move forward in the area of rare disease research and participate at an international level. Keynote presentations on the elements involved in successful research in the area of rare disease were followed by a panel discussion on the barriers, solutions and opportunities in rare disease research.

Participation in European research projects

Ireland contributes, or has contributed, in European rare disease research projects including: AUTOROME, EPOKS, EURAPS, EUROPEAN LEUKEMIA NET, EUROAGENT2, EUROMOTOR, EVI-GENORET, GENESKIN, MANASP, MOLDIAG-PACA, NEUROPRION and NOVSEC-TB.

IPPOSI are consortium partners in the European Patient Academy for Therapeutic Innovation funded by the Innovative Medicines Initiative which will deal with the area of rare diseases.

E-Rare

Ireland is not currently a partner of the E-Rare project.

IRDiRC

Irish funding agencies have not currently committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

This will be addressed as part of the work of the Steering Group for the National Rare Disease Plan at the Department of Health. Protocols for access to orphan medicinal products are under development.

Orphan medicinal product incentives

This will be covered in the National Rare Disease Plan. The approval of Kalydeco for use in Ireland for patients with cystic fibrosis with at least one copy of the G551D gene alteration is likely to be an indirect incentive to support the development of orphan medicinal products. Ireland, through cystic fibrosis centres, played a key role in supporting the phase three clinical trials for this groundbreaking gene modification therapy.

Orphan medicinal product market availability situation

This will be covered in the National Rare Disease Plan.

Orphan medicinal product pricing policy

This will be covered in the National Rare Disease Plan. Orphan medicinal product pricing is decided by the Corporate Pharmaceutical Unit in the Health Service Executive (HSE) and the Health Technology Assessment is conducted by the National Centre for Pharmaco-Economics (NCPE). The appraisal pathway for orphan drugs is

²⁷⁶IPPOSI Information Document on Rare Diseases – 19 February 2009
<http://www.ipposi.ie/index.php/information-centre/rare-diseases>

the same as for other drugs²⁷⁷. In the IPPOSI HTA meeting in October 2012, patient organisations articulated a willingness to get involved in the HTA process at the earliest stage. The Director of the NCPE agreed that this was an area the NCPE are interested in pursuing and indicated that IPPOSI would be an ideal partner in linking his team with relevant patient groups as new applications arrive in to the NCPE office. This type of engagement happened recently with the cystic fibrosis example mentioned above.

Orphan medicinal product reimbursement policy

This will be covered in the National Rare Disease Plan. The reimbursement of medicines in general is provided for through a number of “Community Drug Schemes” and “National High Tech Drug Schemes”. As a result of the 2012 Industry-Department of Health recent supply terms and pricing agreement, a budget for innovative and new treatments was created and it is the view that emerging high cost drugs will fall into this budget.

Other initiatives to improve access to orphan medicinal products

This will be covered in the National Rare Disease Plan. There is no system at present which deals with pricing and reimbursement of orphan medicinal products. The process is the same for all new therapies and treatments in Ireland, all of which undergo a rapid HTA and may then undergo a full HTA. There is no special criteria for orphan medicinal products.

No formal derogation from these general reimbursement schemes exists but individual hospitals may decide to supply a patient with an expensive orphan medicinal product neither reimbursed under the community drugs schemes nor accessible via other schemes. Companies sometimes provide orphan medicinal products to patients free of charge on a compassionate use basis²⁷⁸.

There has been compassionate use of some orphan drugs, for example, in relation to Kalydeco prior to its approval by the Irish government for reimbursement.

Other therapies for rare diseases

This will be covered in the National Rare Disease Plan.

Orphan devices

This will be covered in the National Rare Disease Plan.

Specialised social services

Some non-rare disease specific social services exist in Ireland, such as those provided by the Centre for Independent Living and Personal Assistants Scheme. Other support services and respite care are provided by specific rare disease patient organisations.

1.14. ITALY

Definition of a rare disease

Stakeholders in Italy accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

Although there is no specific national plan/strategy for rare diseases in Italy, they have been designated since 1998 as a health care priority in the context of the 3-year national health plans, which are intended by the national government as directions for actions at a national level, whilst the responsibility for actual implementation of measures is attributed to the regional governments. A coordinated and comprehensive framework of actions has been set up by the Ministry of Health Decree 279/2001, which established a national network for prevention, surveillance, diagnosis and treatment of rare diseases, a National Registry of Rare Diseases, a waiver for medical care cost, a diagnostic work-up and therapy for patients with a suspicion or

²⁷⁷ Also see the Industry-Department of Health 2012 Pricing Agreement which is relevant to all Medicinal Products.

²⁷⁸ EMINET: Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner, May 2011 (pp52-53).

diagnosis of one the rare diseases included in an identified list. The Ministerial Decree 279/2001 established an inventory (*Livelli Essenziali di Assistenza - LEA*) of rare conditions (284 single rare diseases and 47 groups of diseases), which receive specific cost exemption. These diseases are assessed as being chronic, debilitating and requiring a high cost treatment. The LEA lists services provided by the National Health System (NHS) to citizens representing the “essential” services, granted to all Italian citizens or foreigners legally resident in Italy, and they are currently provided after paying a prescription charge as “co-payment”. In accordance with Decree 279/2001, all LEA services are totally free for citizens affected by a rare disease in the list. A major problem is that only a few hundred of rare diseases and some groups of diseases are included in this inventory, which is not regularly updated, denying cost exemption for diseases not included in the list. The act that updates the LEAs, drawn up by the Ministry of Health, has not yet come into force, because the Ministry of Finance is still assessing its feasibility and LEAs remain as first defined in 2001. When effective, the act will allow progress in quality, appropriateness and efficiency, because it includes not only a new list of 110 additional diseases, but also a list of procedures (for example, laboratory assays for the diagnosis of metabolic diseases). Following repeated requests to the Ministry of Health to add specific rare conditions to the list, stakeholders have joined together and circulated in 2012 a petition demanding that diseases not included under the current scheme should be added. Many of these are conditions identified in the most recent years following advancement of scientific and medical knowledge. While certain Regions of the country have recognised and extended care to some diseases not included under Decree 279/2001, rare disease patients in other Regions remain without exemption for co-payment for diagnostics, treatment and care. The Europe-wide petition was launched to bring attention to this issue. On December 2012, the Minister of Health, prof. Renato Balduzzi, has approved the new list of 110 additional single/group of rare diseases and send it for final endorsement to the Ministry of Economy.

A Committee ensures the interregional coordination for rare diseases between the Ministry of Health, the Istituto Superiore di Sanità (ISS – the National Institute for Health - NIH), and all Italian Regions. This Committee has several aims, which include harmonisation of the regional service networks for rare diseases, implementation of the National Registry for rare diseases and management of the list of rare diseases for which patients can obtain free diagnosis and treatment. Rare diseases’ costs are included in the general national health care budget, but €20 million of the total National Health Fund are assigned to rare diseases (art. 1, par. 34 and 34bis, Law dated 23 December 1996, n. 662 and the Agreement between the Government, Regions and the Provinces of Trento and Bolzano, concerning guidelines for the correct use of bound resources by the special statute Regions and Provinces). Until 2010, dedicated funds were available for the implementation of specific projects aimed at strengthening the regional service networks (€30 million for 2008 and €5 million for the following years).

In 2008 the National Centre for Rare Diseases (CNMR) was established at ISS, with the mission of promoting and developing scientific research and public health actions, as well as providing technical expertise and information on rare diseases and orphan medicinal products, aimed at the prevention, treatment and surveillance of these diseases. The CNMR took over the activities carried out for many years by a specific unit within the ISS to tackle rare diseases²⁷⁹.

In 2009, following an agreement between the Ministry of Health, the NIH and the Italian Regions, €8 million were allocated to research projects on rare diseases: €5 million from Ministry of Health and Welfare and €3 million from AIFA (the Italian Drug Medicines Agency).

On 11-13 November 2010 the Italian Federation for Rare Diseases (UNIAMO FIMR Onlus), in collaboration with EURORDIS, organised a national conference on rare diseases²⁸⁰ in Florence in the context of the EUROPLAN project. All stakeholders showed great interest in the sessions and worked together to draw up a final report, whose results were presented during a final plenary session open to the public. The aim was to develop an integrated, global and long term strategy for rare diseases in Italy, with the active involvement of all stakeholders to share common European guidelines. Several drafts of laws focusing on the incentives for research and access to therapies for rare diseases and the production of orphan medicinal products have been presented to the Italian Parliament over the last few years. Their approval lies outside the direct domain of the Ministry of Health.

In 2011 a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a conference was held at the Chamber of Deputies, and a white paper presented, with the aim of

²⁷⁹ www.iss.it/cnmr

²⁸⁰ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf

encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholder into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments and subsequently again to the Ministry of Health for final assessment. The document was illustrated officially in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step is for the document to be commented on by stakeholders. Their comments will be evaluated and implemented into the document by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

On 25 May 2011 the Permanent Conference for relations between State, Regions and Autonomous Provinces of Trento and Bolzano, ratified an agreement, formalising the engagement of health authorities in guaranteeing, through concrete actions, including the global, continuous and homogeneous nationwide management of patients affected by neuromuscular diseases. This goal was achieved via the intensive work carried out by the Ministerial Conference for Neuromuscular Diseases.

The CNMR at ISS coordinated from 2008-2011 the European Project for Rare Diseases National Plans Development (EUROPLAN). The project was co-funded by the EC to promote and implement National Plans or Strategies to tackle rare diseases, to share relevant experiences within countries, linking national efforts with a common strategy at European level. This “double-level” approach ensures that progress is globally coherent and follows common orientations throughout Europe. These activities continue under the EUCERD Joint Action with the main goal of establishing an international and interactive network of stakeholders (mainly policy makers) to speed up the elaboration and the implementation of Rare Diseases National Plans/Strategies, through scientific and technical assistance, workshops and the active participation of patients Groups (EURORDIS and National Alliances). In 2012 a group of key indicators for National Plans on Rare Disease was selected to be considered by the EUCERD with a view to adopting a recommendation in this area.

Centres of expertise

In 2001, the Ministerial Decree 279/2001 foresaw the establishment of a national network for rare diseases (Rete Nazionale delle Malattie Rare), made up of hospitals and referral centres, for around 500 rare diseases, those included in the aforementioned list (LEA). Soon after the delivery of the Ministerial Decree, the Italian Constitution was changed, and health programmes and their organisation were delegated to the Regions. Because of their autonomy, the 20 Regions used different criteria to identify centres for rare diseases and adopted different models to organise their networks. Around 215 centres have been identified.

According to the n. 279/2001 decree, each patient suspected to be affected by a rare disease is addressed to designated hospitals where a free of charge diagnosis can be achieved and, if the disease is confirmed, free treatment is offered by any hospital or outpatient facility within the NHS. Coordination centres have been created at regional level in order to manage the activities of referral centres, to exchange information between them, and to provide expertise and data to the regional rare disease registries.

In 2011, UNIAMO F.I.M.R.²⁸¹ developed the project “A Community for Rare Diseases”, aimed at defining a model to assess the quality of expertise centres for rare diseases in Italy. The project gathered all relevant stakeholders who reached a common definition of a Centre of Expertise.

Registries

The Italian National Registry for Rare Diseases, was established at ISS in 2001 in agreement with article 3 of the Ministerial Decree 279/2001. It is located at Italian CNMR– ISS and it is supported by public funds. The general objectives are epidemiological surveillance of rare diseases and national and regional planning of measures to assist rare disease patients. Specific objectives include the following: i) estimation of incidence and prevalence; ii) temporal and geographical distribution of cases and diseases at national level; iii) diagnostic delay. The legal provisions envisage the Registry as a tool to support scientific research in the clinical, biomedical and epidemiological fields. The National Registry collects the data coming from Regional registries. From 2001 onwards each Italian Region established its own registry for rare diseases. These registries collect epidemiological information provided by accredited Centres for rare diseases (Presidi) and every 6 months they send the agreed common data set to the National Registry. The Regional Registries differ in their internal organisation, aims and collected information. Some of them have mainly epidemiological and public health

²⁸¹ <http://www.uniamo.org/>

purposes to support regional planning, while others are aimed at evaluating health services and diagnostic procedures. Agreements have been established between regional administrations in order to create interregional registries. These registries have been established between Piedmont and Valle d'Aosta, and between Veneto and Autonomous Provinces of Trento and Bolzano, Emilia-Romagna, Liguria, Campania and Puglia. Each interregional system has its informatics infrastructure, acting as a network connecting different centres involved in the management of patients with rare diseases.

On November 2011 the CNMR-ISS published the first Report on "National Registry and Regional/Interregional Registries for rare diseases"²⁸², describing the surveillance system for rare diseases in Italy. In addition to a background of European initiatives on rare diseases, this Report also provides detailed information of the evolution of Italian regulatory and institutional context; the steps towards planning and implanting the National Registry; a description of regional/interregional registries; the data quality assessment; the methodological models for estimating epidemiological indicators. The National Registry provides a tool for epidemiological surveillance of rare diseases and evaluating health care programs. The Registry has a strong legal support and its aims are connected with the exemptions from the costs associated with the delivery of care; is a web-based registry in compliance with the legal and ethical requirements; is a population-based registry, although the regional coverage is heterogeneous; provides important public health indicators. The National Registry is linked to other interregional, regional and international registries.

A congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome on 22 February 2012, to illustrate the results, to discuss and agree among all actors on actions to improve further the performance of the National Registry.

The CNMR is also providing support to spontaneous independent registries promoted by patients and run by clinicians: in the last years the Italian Registry of Paroxysmal Nocturnal Haemoglobinuria and Cystic Fibrosis have been established, with the assistance of CNMR. Registry initiatives for rare diseases will be a focus of the future National Plan for Rare Diseases.

Italy also participates in European registries such as EUROCAT, EIMD, EURO-WABB, EuroWilson, TREAT-NMD, HAE-registry, RBDD, AIR and EUROCARE CF.

Neonatal screening policy

In Italy, neonatal screening is mandatory for cystic fibrosis, congenital hypothyroidism and phenylketonuria (Law 104, 5 February 1992). Some Regions perform screening of additional diseases including adrenal hyperplasia, biotinidase deficiency, maple-syrup urine disease, and galactosaemia. Other Regions, including Tuscany, Sicily and Emilia Romagna, adopted wider neonatal screening programs to include a number of metabolic disorders, based on the guidelines developed by scientific societies. According to SIMMESN (Società Italiana per lo Studio delle Malattie Metaboliche Ereditarie e lo Screening Neonatale²⁸³), about one fifth of the Italian newborn population underwent an expanded screening in 2011. UNIAMO F.I.M.R. sent a position paper on this subject as Memorandum for the XII Social Affairs Commission of the Chamber of Deputies on Draft Law No. 5,440 Conversion into law of Decree-Law of 13 September 2012, n. 158 laying out "urgent measures to promote the development of the country by a higher level of protection of health", calling for a gradual expansion of neonatal screening programs for all rare diseases for which there is evidence of appropriateness and not just to rare diseases for which a cure already exists. However, it will be mandatory to define a common set of standards, procedures and methodologies at the national level to ensure an effective, fair and appropriate disease screening as well as to assure adequate health and social post screening management.

At European level, the "Tender on EU newborn screening practices" had the aims of identifying and evaluating all aspects deemed relevant to the implementation of a public health action in newborn screening (NBS), taking into consideration the views of professionals, patients and health authorities. This project, funded by European Commission DG SANCO, was coordinated by CNMR-ISS, with the intent to support actions at the Community level, to identify the strategies which the European Commission could adopt to promote the establishment and improvement of NBS programmes in EU. All relevant documents elaborated by the Tender and the final reports are available at the www.iss.it/cnmr website. In line with the results obtained during this Tender, in 2011 the Italian Ministry of Health funded a project on neonatal screening aimed at harmonising access to health services in the Italian Regions. The project, coordinated by the CNMR-ISS, is carried out in collaboration with the Ministry of Health, the Italian Agency for Regional Health Services (Age.Na.S), the Tavolo Interregionale Malattie Rare, and two Italian Scientific Societies (SIMMESN and SIGU).

²⁸² <http://www.iss.it/binary/publ/cont/undici20WEB.pdf>

²⁸³ www.sismme.it/it/documents/rt_screening/rt_screening_2011.pdf

Genetic testing

In an international context, Italy is one of the few countries to monitor genetic test use (this survey was implemented in the 1980s), and recently this monitoring has expanded to include clinical and laboratory activities carried out by Medical Genetic Institutes and also private laboratories since 2009^{5,6}. This census, promoted by SIGU, surveys the services provided by Italian Medical Genetic Centres and involves the NHS bodies, the IRCCSs (Excellence Centres for Healthcare and Research), the University Institutes, the CNR (Research National Council) laboratories, and private laboratories. Data collection takes into account the typology of the Institutes, number and functions of the laboratory staff, cytogenetic analyses, genetic-molecular and immunogenetics analyses, and clinical activities, including genetic counselling. Certified quality systems adopted by the Institutes and the adequacy of some genetic tests have been also checked.

The survey concerning the 2011 data was carried out in 2012. The census was made possible thanks to the collaboration of the Bambino Gesù Children Hospital, Orphanet-Italy, and SIGU. On the whole, 517 services hosted by 268 Hospitals or Institutions were surveyed, including 145 clinical genetic services, and 153 cytogenetic, 198 molecular genetics and 21 immunogenetics laboratories. The 53% of services are located in the Northern regions, the 20% in the Central regions, 17% in the Southern regions, and 10% in Sicily and Sardinia. About 74% of these services were accredited and 55% certified.

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. This scheme includes molecular and cytogenetic tests and has been addressed to public laboratories which provide genetic tests. This activity is dependent on a Steering Committee, composed of experts who evaluate the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, this scheme was extended also to private genetic laboratories. A Steering Committee, composed of experts, evaluates the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, a fee for participation was introduced by a national decree for all participant public and private laboratories. At the end of each trial of external quality control, each laboratory receives its own results. In addition, the CNMR-ISS organises a national Conference to illustrate the main results. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme. In particular, as regard molecular genetics, in 2012, national experts have assessed laboratory performance on genotyping, interpretation, and reporting of test results for a total of 404 different DNA samples sent to 68 public and private laboratories. In addition, 75 laboratories participated in one or more schemes of constitutional or cancer cytogenetic quality control.

The CNMR-ISS is a member of the management board of the European Molecular Genetics Quality Network (EMQN²⁸⁴), a not-for-profit organisation promoting quality in molecular genetic testing by establishing, harmonising and disseminating best practice. EMQN provides external quality assessment to labs worldwide in collaboration with other organisations, including EuroGenTest, CF Network, ESP, UKNEQAS for Molecular Genetics, RCPA QAP, and the EAA.

Genetic tests for 1042 genes and 1107 diseases are registered in the Orphanet database²⁸⁵.

National alliances of patient organisations and patient representation

In Italy, UNIAMO F.I.M.R is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing more than 600 rare diseases. UNIAMO publishes a newsletter and organises regular meetings and conferences. The goal of this Federation is to serve as a reference and representative voice for rare diseases, bringing opinions of patients and their families in the public health decision-making processes at regional and national level. It is committed in the protection of patients' rights and improvement of the quality of life of rare disease patients and their families. UNIAMO is currently organising Regional Delegations: a coordination of territorial groups in order to develop or strengthen the relationship of solidarity and cooperation between member organisations and to foster, at local level, initiatives and policies promoted by the Federation. The Federation participates in the regional boards on Rare Diseases of Apulia, Liguria, Lazio and Lombardy regions. In addition, UNIAMO F.I.M.R. has played an important role in the Lombardy Region, in particular during the discussion of rare disease diagnostic and therapeutic pathways, having been enrolled by patients lacking reference associations on the territory.

In 2012, a framework agreement was signed by UNIAMO F.I.M.R. with the Telethon Foundation Onlus-

²⁸⁴ <http://www.emqn.org/emqn/Home>

²⁸⁵ Information extracted from Orphanet in December 2012.

CTFO, to promote access to TNGB genetic biobanks by members of the associations' federation.

In October 2012, the Ministry of Welfare recognised UNIAMO F.I.M.R. as an Association of Social Utility.

There is no public funding scheme for activities of the patients' organisations, but national governmental institutions (e.g. the Welfare Ministry) and local institutions support specific actions. Grants for activities of patients' organisations are coming mainly from private sponsorship, charities and income tax donations. UNIAMO's goals for 2010-2012 were reached taking advantage from these funds, which have granted continuity to the Federation's activities, and sustained several projects:

- "Knowing to assist", carried out in collaboration with Farindustria and Scientific Societies, is aimed at training general practitioners and paediatricians regarding rare diseases. The project is based on a covenant of understanding signed by several Institutions. The project will cover the whole Italian territory by 2013.
- "Galeno Help" results from a memorandum of understanding between UNIAMO F.I.M.R. and the professional pharmacists' federation (UPFARM), with the intention of giving practical support to patients who need drugs which are difficult to find. Many of these drugs can be prepared in the galenic laboratories of the pharmacies in a personalised manner. "Galeno Help-Pharmacist helps for rare disease patients" is a national service offering the possibility to quickly and easily find the nearest participating pharmacy.
- "Mercury", funded by the Ministry of Labour and Social Affairs in cooperation with the signatories of the aforementioned covenant of understanding, has been designed to train the general practitioners and paediatricians in rare diseases. The major goal of the project is to implement and enhance the web site "Malatirari.it" and turn it into a platform to meet the rare disease community's needs along the complex path from a suspected case to diagnosis of rare disease. The site will become a virtual place where information based on direct experience can be shared by patients, relatives and health professionals involved in the diagnosis and treatment of these diseases. In 2012 the data were implemented with an area dedicated to health professionals, with a restricted access.
- "The Atlantis Code" is aimed at fostering the culture of research in rare diseases. Developed in partnership with the Telethon Foundation, it involves rare disease patient organisations in the attempt to identify research priorities and provide answers to the patients' needs. Three seminars were organised. The outcomes of this survey were matched up with the results of a similar investigation carried out by EURORDIS at European level.
- "Momo" intends to bring together, with a unique voice, the demands of different groups of rare disease patients at Regional level. For this purpose, regional UNIAMO delegations were created in the context of a progressive regionalisation of the federation.
- "A Community for Rare Diseases", is aimed at developing a model to assess the quality of expertise centres for rare diseases in Italy. Since many Regions are reorganising their network of expertise centres, it was felt important to share similar inclusion criteria. Participants were the Ministry of Health, the Ministry of Labour and Social Affairs, ISS, Regions, local health authorities, Orphanet Italy, expert centres, municipal districts, general practitioners, primary care paediatricians, biobanks and patients organisations. On September 20, 2012 an agreement was signed with Age.Na.S., the National Agency for Regional Health Care Services, for the implementation of the second phase of the project which will assess some previously defined centres of expertise, with a major emphasis on the geographic distribution of a selected group of centres dedicated to distinct diseases (e.g. haemoglobinopathies).
- "Diaspro Rosso", a pilot project concluded in 2012, has provided an accurate, effective and efficient model for detecting the care needs and the social-economic costs for families with patients affected by rare diseases. The model will be presented to the institutional actors as a decision-making tool to be used to develop policies on social health based on concrete data.
- "Dumbo" was aimed at developing a model for the social reporting of patients' organisations. This model was illustrated to the Associations' members in several meetings and UNIAMO F.I.M.R. used it to present its first Social Report.

In September 2006, the National Council for Rare Diseases (the "Consulta") was established as a national independent representative body and its activities were hosted by the CNMR-ISS. It was originally composed of 34 members (one for each participating rare disease patient organisation), which was then lowered to 28; these members were elected by 264 rare disease patient organisations' representatives. The Consulta aimed at identifying the priorities in the field of rare diseases, to define the problems, to recognise solutions for the

patients and their families, to involve rare disease patients in the legislative bodies' decisions, and to strengthen the links between RD organisations and the society. By the end of 2010, the Consulta²⁸⁶ constituted itself as a private legal organisation which keeps on executing the tasks entrusted by the Minister of Health and affords some of the daily problems of rare disease patients.

The Council for Neurodegenerative Diseases was established by the Ministry of Labour, Health and Social Affairs, through a Ministerial Decree (27 February 2009). The Council brings together patients organisations for neurodegenerative diseases, such as amyotrophic lateral sclerosis, muscular dystrophy, spinal muscular atrophy, advanced stage muscular dystrophy and locked-in syndrome, experts on these disorders, and representatives from Regions and the Ministry of Health. Based on the final document produced by the Council, a proposal for an agreement among State and Regions on health care pathways has been drawn up and is currently assessed by the Regions.

The Veneto Region issued a call in March 2010 for the provision of contributions to Social Promotion Associations, for projects and initiatives identified in several areas of interest, including initiatives aimed at increasing the awareness and knowledge of rare diseases. Several of these projects have been funded in 2011.

In November 2012, the MIR (Movimento Italiano dei Malati Rari) was established by 15 patients' associations.

Sources of information on rare diseases and national help lines

Orphanet activity in Italy

Since 2001, a dedicated Orphanet team was established in Italy, which is hosted by the Bambino Gesù Children Hospital in Rome. This team is in charge of collecting data on rare diseases-related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations, networks) for entry into the Orphanet database. This group was designated in 2010 by the Ministry of Health as the official Orphanet team for Italy. The Orphanet portal is available in Italian and the team also maintains the Orphanet Italy national website²⁸⁷.

On the occasion of the tenth anniversary of Orphanet Italy, an updated Italian Directory of Services, *Annuario Orphanet delle Malattie Rare 2011*, was presented at the Ministry of Health. In attendance was Italian Health Minister, as well as the Director of the Paediatric Hospital Bambino Gesù, hosting the Italian Orphanet headquarters; Orphanet country coordinator and Scientific Director at Paediatric Hospital Bambino Gesù; President of Farmindustria, which financed this second book; and President of UNIAMO F.I.M.R.

In December 2011, the Italian Minister of Health, Prof. Renato Balduzzi, presented the "Relazione sullo stato sanitario del paese 2009-2010" (Report on country sanitary status 2009-2010). For the very first time, the Italian Ministry of Health identified Orphanet as a reference source for rare diseases and orphan drugs, stressing the relevance of the joint action established between the Ministry of Health and Orphanet-Italia.

In May 2011, Orphanet Italy signed a collaboration agreement with *Fondazione Cesare Serono* linking the two web sites in order to spread information on rare diseases to a broader public.

From September 2011 onwards the Italian Society of Anesthesia, Analgesia and Intensive Paediatric Care (SIAATIP) collaborates with Orphanet Italy to develop the "Orphanet Emergency" guidelines, designed to improve the hospital emergency management of rare diseases, through recommendations about the care of patients who need medical treatment under emergency.

Official information centre for rare diseases

The Ministry of Health organised a specific section for Rare Diseases²⁸⁸, providing several information, including the list of rare diseases present in the ministerial decree 279/2001.

The CNMR-ISS plays a key role in disseminating information on rare diseases through the official website²⁸⁹ and the Italian national helpline for rare diseases "Telefono Verde Malattie Rare". The website (in Italian and English), updated weekly, is addressed to health operators and institutions, social workers, associations, patients and their families and, in general, the wide public. The site has been structured on two levels: the central site containing general information, and satellite websites containing specific projects and different topics, including Registries (Italian National Registry for Rare Diseases, Italian National Registry for Orphan Drugs, Italian National Registry for Congenital Anomalies), Orphan drugs, Guidelines, Narrative medicine, Folic Acid Italian Network, European projects, Genetic Tests, Patient Organisations. The section "Centres for rare diseases in Italy" lists all Centres accredited by Regions for diagnosis and treatment, which

²⁸⁶ www.cndmr.it

²⁸⁷ <http://www.orphanet-italia.it/national/IT-IT/index/homepage/>

²⁸⁸ <http://www.salute.gov.it/malattieRare/malattieRare.jsp>

²⁸⁹ www.iss.it/cnrmr

can be searched by disease, code number, Region, etc. Moreover, all contact details of the Regional Coordination Centres are available.

Help line

The Italian national helpline for rare diseases “Telefono Verde Malattie Rare” (no. 800.89.69.49) was set up at CNMR-ISS on February 2008, and is funded by the Ministry of Health. This helpline collaborates with all stakeholders, including the Ministry of Health for legislative and regulatory issues, and it is advertised on the CNMR-ISS web page²⁹⁰. The line is free and available five days per week (from 9 am to 1 pm). From abroad it is possible to access the line information by using the e-mail address tvmr@iss.it. A group of psychologists, sociologists and medical doctors trained and experienced on telephone counselling, public health policies and management of rare diseases are involved in this activity. The aim of the service is to inform health operators, social workers, patients and their families, and the public at large, on rare diseases (including exemptions from the costs of medical care in Italy), and to address them to the national/Regional network of specialised centres. *Ad hoc* literature researches are performed for specific questions. Information about patient organisations, orphan medicinal products and clinical trials running in Italy and abroad are also provided. A web based system is used for data collection and to provide information, also using national and international databases (e.g. Orphanet, PubMed, ClinicalTrials.gov, etc.). The Italian national helpline for rare diseases is a member of the European Network of Rare Disease Help Lines.

In 2012, the CNMR-ISS started collaborations and training activities for regional help lines (i.e. Contact Centre of Tuscany Coordination Centre for rare diseases) and with Patients’ Associations (i.e. Foundation “W Ale –Alessandra Bisceglia”).

Other sources of information on rare diseases

Information for patients and health professionals is also provided by websites run by Centres for rare diseases present in some Regions. A specific e-mail address (esenzioni@sanita.it) at the Ministry of Health provides information on issues concerning LEA services and co-payment exemption for rare disease patients. Online Regional information is also available. Other services are run by patient organisations and are largely heterogeneous in their coverage.

The website www.malafirari.it set up by UNIAMO F.I.M.R., provides both general information on legislative and administrative issues and orphan medicinal products, and, at regional level, specific information managed in collaboration with patients’ organisations and health professionals.

Many regions have developed their own websites dedicated to rare diseases, as well as help lines for health operators and patients.

On December 2011, OrphaNews-Italia¹³ was launched by the national Orphanet team. This online bulletin offers a complete translation into Italian of the contents of OrphaNews-Europe, and is available from the homepage of Orphanet-Italy and also from the Orphanet Italian country site. The issues of OrphaNews Italia are published online on a regular basis, one week after the publication of the English version. At the end of 2012, 18 issues had been published with a total number of 2465 registered users.

Best practice guidelines

The Ministry of Health and ISS are involved in the National Guidelines System (NGS), which is officially entitled to issue guidelines and to make available any other document drawn up by the Consensus Conferences carried out by NGS. Guidelines published by CNMR-ISS, as part of NGS, include those for Down’s syndrome, alternating hemiplegia, hereditary epidermolysis bullosa. Guidelines for tuberous sclerosis and aniridia are under development.

In order to promote the development of high quality best practice guidelines and their use in Italy and across Europe, CNMR-ISS organised national and international training courses (9-11 July 2012) providing participants (health care professionals, policy makers, patients) with the opportunity to learn about the core methodology used to develop best practice guidelines. In addition, CNMR-ISS encourages international debate on the role and quality of best practice guidelines in the field of rare diseases. In particular, a workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, aimed at sharing experiences and knowledge and discussing critical methodological issues due to the specificity of rare diseases.

In 2012, CNMR-ISS, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices (www.rare-bestpractices.eu), commencing in January 2013. This project

²⁹⁰ www.iss.it/cnmr

will bring together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health.

About 85 *Percorsi Diagnostico-Terapeutico-Assistenziali-PDTA* (Diagnostic Therapeutic Care guidelines) dedicated to diagnosis, treatment and clinical management of rare diseases have been developed since 2010 by the Lombardy Region²⁹¹.

The working group of the National Committee for Bioethics (CNB) and the National Committee for Biosecurity, Biotechnology and Life Sciences (CNBBSV) published two reports in 2010 dealing respectively with the issues related to the long storage of biological samples obtained by neonatal screenings, and susceptibility testing and personalised medicine. In 2011, the CNB drafted a document relating to orphan medicinal products for people with rare diseases²⁹².

Training and education initiatives

In Italy, a second level Master degree in rare diseases is organised by the University of Turin. Rare diseases are present in the undergraduate training and post-graduate courses of the Optional Integrated Degree Course of Medicine and School of Specialisation at the Universities of Padua, Siena and Pisa.

The CNMR-ISS organises residential courses and learning activities dedicated to the empowerment of patients, health professionals and policy makers²⁹³. This program is included within the project "Rare diseases: from monitoring to training" funded by the Ministry of Health.

The CNMR and ISS External Relations Office have developed in several Regions a project for training the general practitioners (GP) and paediatricians to look for rare diseases, in order to reduce delay in diagnosis, to manage patients' care appropriately in the framework of the Italian rare diseases network, and to improve communication skills. To reach this goal, the courses employ an interactive method, Problem-Based Learning (PBL). PBL is an instructional approach that uses a problem as a didactic initial stimulus; learning is achieved by working in small groups assisted by a trained PBL facilitator at the explanation or solution of the problem. The GPs' and paediatricians' participation to the courses has been active and all professionals got positive results in learning assessment questionnaires; ratings reported in satisfaction questionnaires were mostly positive. The training showed that PBL enhances participant activity and provides the opportunity to practice skills, so that they can produce changes in professional practice, and, ultimately, in health care outcomes. In order to improve the training model, patient organisations were involved in new courses, in collaboration with the "W Ale - Alessandra Bisceglia" Foundation, aiming at training GPs and paediatricians on congenital vascular malformations.

A workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

A major role in educating medical doctors is carried out by patients' organisations (e.g. UNIAMO-F.I.M.R. through the projects "Knowing to assist" and "Mercury", see the "National alliances of patient organisations and patient representation" section).

The Italian Telethon Foundation and Orphanet-Italy joined their respective competences and contact networks in October 2012 to meet the patients' needs and support health professionals via a training course entitled "e-patients, e-parents, e-doctors: le malattie rare via web – opportunità e rischi". Suited for all stakeholders of the rare disease community, this event provided an opportunity to discuss web services and social networks as tools for professionals, patients and their families. During the course, health professionals, journalists, and IT experts presented their experiences to guide the community in using the web as a tool to break the isolation rare diseases can impose. A round table was animated by communication experts on the responsible use of Internet.

On 16 April 2012, the Orphanet team held a training course in Rome for health professionals operating in the Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

National rare disease events in 2012

Since February 2008, UNIAMO F.I.M.R. coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farindustria, the Serono Foundation and Novartis. Awareness has been achieved through over one hundred local events, in squares, sports halls and schools and through many

²⁹¹ <http://malattierare.marionegri.it/content/view/111>

²⁹² http://www.governo.it/bioetica/pdf/Malattie_rare_25112011

²⁹³ <http://www.iss.it/cnmr/appu/index.php?lang=1&tipo=56&anno=2011>

articles and interviews on rare diseases in newspapers and on TV. The cartoon "Mamma , cosa sono le malattie Rare? – Mum, what are rare diseases?" promoted by UNIAMO F.I.M.R. was shown on Mediaset TV Channels all through February. The Volley Major League collaborated with UNIAMO F.I.M.R. in distributing dedicated information leaflets on rare diseases during the matches where an awareness raising announcement was also made.

On 29 February 2012, the event "La solidarietà che costruisce" was organised at the Italian Senate to promote the Rare Disease Day in Italy, with the participation of several leading figures in the field of the rare diseases. This event raised awareness on the needs and actions in the field of rare diseases, and promoted dialogue between stakeholders and public institutions. During the event, Orphanet-Italy received a prize for its contribution in the "Mercurio" project (update of the malatirari.it web site) managed by UNIAMO F.I.M.R.

To mark Rare Disease Day, the Bambino Gesù Children Paediatric Hospital, in collaboration with Orphanet launched on 27 February 2012, a pilot project on rare diseases for middle schools. The "Virgilio" public school is hosting the project whose aim is to teach children the basics of familial inheritance. Professionals from Bambino Gesù Hospital will work together with teachers and pupils to produce papers, which will be evaluated in the context of a prize-awarding contest. The award ceremony will be held on Rare Disease Day 2013.

The CNMR-ISS presented two different events: a theatre play dedicated to rare diseases, inspired by real events, and the fourth edition of the event "Il Volo di Pegaso - Raccontare le malattie rare: parole e immagini" (Pegasus' Flight – Describing rare diseases through words and images), an art contest on rare diseases. The theatre play "Controvento" (Against the Wind) took place at the Quirino theatre in Rome on 27 February 2012 and the art contest prize-giving at the ISS on the same day. Another institutional event, on 29 February was the initiative "La solidarietà che costruisce" (Creating through solidarity): several leading figures in the field of the rare diseases discussed the topic "L'esperienza, il presente e il futuro per le Malattie Rare in Italia", while a white book "Una incompiuta: le Malattie Rare" was presented by the Senator Antonio Tomassini. Flash mobs were also organised to mark the Day with a closing speech by the Italian Minister of Health, Prof. Renato Balduzzi.

On 29 February 2012, the patient association MITOCON organised a round table focused on research, care and policy concerning rare diseases.

On 8 February 2012, in the Rome Campidoglio a press conference was held for the event "Stammi vicino" (Stay close to me), organised by EEC syndrome International Network Word Communication ONLUS. This event, aimed to foster communication on rare diseases through sport.

On 18 February 2012, on the occasion of the Del Monte Italian Cup final tour, before the beginning of the matches, particular attention was given to the importance of funding rare disease research.

On 4 June 2012, an international congress entitled "Narrative Medicine and Rare Diseases" was held in Rome at the ISS.

On 12 June 2012 a press conference was held at the Senate to mark the launch of the book "Malattie rare: alla ricerca di un approdo" (Rare Diseases: in search of a landing place). This book collects the results of the Public Consultation launched in March 2012 on website and includes interviews of the main Italian and European stakeholders belonging to the academic and institutional world, together with the experience of patients and their families. The aim was to provide input on the elaboration of the National Plan for Rare Diseases.

On 12 July 2012, a press conference was organised in Rome to launch the second edition of the project "MALattie raRE NOSTRUM", promoted by "Tender to Nave Italia", a non-profit foundation and the Bambino Gesù Children Hospital. The project aimed at making a group of children affected by rare diseases more independent, fostering sea and navigation as an education instrument.

From 1 September to 6 September 2012, the first edition of the project "GiRare Mangiando", an initiative of the non-profit organisation UNIAMO Goldin, was held in Venice. This project was designed to provide an information path of independent living for patients affected by metabolic rare diseases. Four young patients were given the opportunity to stay in an apartment in Venice owned by UNIAMO Goldin, profiting by the facilities of the Fantasia restaurant, managed by rare disease patients, and following a program of cultural activities on the territory. The young participants have been supported by the healthcare professionals of the Bambino Gesù Children Hospital.

On 18 September 2012, a conference entitled "The State of Art of Rare Diseases: Rare Diseases and Economic Development" was held in Rome at the Ministry of Health. The Conference focused on several issues related to rare diseases: diagnostic difficulties; lack of therapeutic options and structured care pathways; chronic and debilitating course of the disease; emotional impact due to feelings of isolation experienced when

living with one of these diseases. The initiative aimed to identify goals and actions to support health services, industry production and drug companies.

Several dozens of events have been organised locally in all Italian Regions.

Hosted rare disease events in 2012

Amongst the events announced in *Orphanews Europe* were: 15th Biannual Meeting of the European Society for Immunodeficiencies (Florence, 3-6 October 2012), EpiRare International Workshop: Rare Disease and Orphan Drug Registries (Rome, 8-9 October 2012), Goldrain Courses in Clinical Cytogenetics and Prenatal Genetic Diagnosis (Goldrain, 15-21 September 2012).

Research activities and E-Rare partnership

National research activities

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)²⁹⁴, Ministry of Health and ISS. Funds for rare diseases research are provided by Ministry of Health, ISS, AIFA and Ministry of Education, University and Research, Telethon, patient organisations and a few charities. The last Health Ministry call for projects for rare diseases²⁹⁵ had a total budget of €8 million. The call for projects was published in 2008 and 13 projects were granted in 2010.

A bilateral agreement between Italy (ISS) and USA (NIH) was established with the purpose of developing and increasing research in different fields, including rare diseases since 2002. This agreement is still active.

AIFA issued calls to fund independent researches on the development of orphan medicinal products. In particular, AIFA financed a three-year initiative, launched in 2005, to support clinical research on drugs of interest to the NHS where commercial support is inadequate: one of the concerned areas was the field of rare diseases and orphan medicinal products. Three topics were included in the clinical research area concerning rare diseases: the benefit-risk profile of orphan medicinal products designated by EMA; the benefit-risk profile of off-label drug use (and in particular generics); the benefit-risk profile of drugs for non-responders to standard treatments. Projects in these topic areas were funded for up to a maximum of €300,000, with the therapy costs funded separately. From 2008 onwards rare diseases and orphan medicinal product research is being funded by the Ministry of Health, within the general health research call, with a specific budget reserved for rare diseases research. A specific call to fund research projects on rare diseases was issued by the Ministry of Welfare in 2009.

In 2012 Telethon was able to fund 260 research projects on rare genetic diseases, thanks to the fundraising activities in 2011.

Foundations and associations promote campaigns funding genetic research or research on specific diseases. Voluntary funds can be collected through general taxation.

Participation in European research projects

Italy participates, or has participated, in European rare disease research projects including: AAVEYE, ADIT, ANTIMAL, BIG HEART, BIOMALPAR, BIO-NMD, CELL PID, CARDIOGENET, CUREHLH, CUREFXS, CLINIGENE, CONTICANET, CSI-LTB, DYSCERNE, DRUGSFORD, DEMCHILD, EUROPEDICAT, EUROMOTOR, ESPOIR, EUROSARC, ENRAH, EURADRENAL, EUCILIA, EUCLYD, EMSA-SG, EUROBONET, EUROGROW, EURO-LAMINOPATHIES, ENCCA, EUROPAPNET, EUROBNFS, EURENOMICS, EURO-CGD, EURO-SCAR, EUROTRAPS, EURPIFNET, EUROSD, EPINOSTICS, ERMION, EUROGEBETA, EURORETT, EUROPSPA, EUMITOCOMBAT, EURAMY, EURAPS, EUREGENE, EUROCARE-CF, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, GENOMIT, INHERITANCE, IMMOMECA, INTRALL, IPF-AE, HAE III, GRIP, IMPACTT, FIGHTHLH, HMA-IRON, HSCR, KINDLERNET, NEUROMICS, MTMPATHIES, LEISHMED, LIGHTS, MALARIA AGE EXPOSURE, MANASP, MITOCIRCLE, MOLDIAG-PACA, MCSCS, MILD-TB, MM-TB, MYELINET, MYORES, MTMPATHIES2, NANOMYC, NEUROKCNQPATHIES, NEUROPRION, NEUROPROMISE, NEUROSIS, NMD-CHIP, NSEURONET, OSTEOPEPE, OPTATIO, OVERMYR, PEROXISOMES, PNSEURONET, PROTHETS, PODONET, PEMPHIGUS, RARE-BESTPRACTICES, RD PLATFORM, RDCONNECT, RISCA, READ-UP, SIOPEN-R-NET, SKIN-DEV, SPASTICMODELS, SME MALARIA, STEM-HD, TAMAHUD, TUB-GENCODEV, TARGETHERPES, TIRCON, VITAL, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPATH.

²⁹⁴ <http://www.agenziafarmaco.gov.it/>

²⁹⁵ http://www.quotidianosanita.it/cronache/articolo.php?&&articolo_id=1144&&cat_1=1&&cat_2=0

E-Rare

Italy, represented by ISS, is a partner of the E-Rare project and took part in all three Joint Transnational Calls. Italy participated in 12 of the 13 consortia selected for funding by the first call. In the second E-Rare transnational call, Italy participated in 8 of the 16 consortia/projects selected for funding with a budget of about €1 million. Italy participated in the 3rd Joint Transnational Call in 2011 and Italian teams have been funded to participate in 7 of the selected consortia. Italy did not take part in the 4th Joint Transnational Call in 2012.

IRDIRC

The ISS and Italian Telethon Foundation are committed members of IRDiRC.

Orphan medicinal products^{296,297}

AIFA is the main body in charge of the introduction of orphan medicinal products into the Italian market. The National Registry of Orphan Drugs includes data on diagnosis and follow-up of patients treated with orphan medicinal products. These drugs are authorised at central level by EMA (European Medicines Agency) and reimbursed by NHS. The National Registry of Orphan Drugs, established by AIFA and managed in collaboration with the National Centre for Rare Diseases, surveys forms for each rare disease and its related drugs, and collects, checks and analyses data sent by Regional Centres authorised to distribute these drugs. The goal of the registry is to have a nationwide coverage, to address all Italian Centres qualified to distribute and prescribe orphan medicinal products.

Orphan medicinal product committee

There is no specific orphan medicinal product committee at national level in Italy.

Orphan medicinal product incentives

AIFA has established an innovative funding scheme (Fondo AIFA 5%). Established under Article 48 of Law 326/2003 and operative since 2005, the Italian pharmaceutical companies are required to donate 5% of their promotional expenditure to an independent research fund. The fund collects €45 million each year: half of this allowance is used for the reimbursement of orphan and life-saving drugs awaiting market entry, while the other half is aimed at supporting independent research, drug information programs and pharmaceutical vigilance. This funding program for independent clinical research on drugs is open to researchers working in public and non-profit institutions. One of the research areas of the program is dedicated to orphan medicinal products for rare diseases. At the beginning of 2009, three calls for proposals (2005-2007) had been finalised and 69 studies received funding in the area of rare diseases. Since 2008, however, rare diseases and orphan medicinal product research were not listed among the priority areas.

Orphan medicinal product market availability situation

In Italy, 47 out of the 72 orphan medicinal products approved by EMA are launched on the market. The cost of 44 of them is fully paid by NHS, based on a therapeutic indication, while 3 of them are reimbursed under special circumstances (Law 648/96). The other EMA approved drugs have a pending request at AIFA by the companies in charge of pricing and reimbursement²⁹⁸. A list of orphan medicinal products with European marketing authorisation and the date of their publication in the Official Gazette concerning their marketing in Italy is available²⁹⁹.

Orphan medicinal product pricing policy

Prices of all medicines for reimbursement by the NHS, including hospital-only drugs, are set by AIFA. Two interministerial committees are involved in this process, the Pricing and Reimbursement Committee and the Technical-Scientific Commission¹⁵.

²⁹⁶ This section has been written using information from the KCE reports 112B: *Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* pp.49-53.

²⁹⁷ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision pp.15-16.

²⁹⁸ According to the Final Report of the Europlan National Conference, 11-13 November 2010.

http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf p16.

²⁹⁹ http://www.iss.it/binary/orfa/cont/Farmaci_orfani_in_Italia_Feb_2009.pdf (document accessed May 2011 and last updated in February 2009).

Orphan medicinal product reimbursement policy

In Italy drugs are catalogued in A and C classes, depending on their reimbursement. Costs of class A drugs are totally paid by NHS and free of charge for citizens, while class C drugs are paid entirely by patients. Many Regions in the last years have supplied class C drugs to their population, while other Regions, bound to strong budgetary limits and measures to contain their health care cost levels and trends, have been forced to not provide extra LEA services to their citizens, including C Class drugs. Reimbursement is granted for all orphan medicinal products which follow the centralised marketing authorisation procedure. Moreover, for all drugs which are not currently classified in class A, reimbursement is regionally based within “extra LEA services”, which means further services decided by the individual Regions and covered by their own economic resources. According to AIFA, the cost of orphan medicinal product raised in 2012 to about €735.00.000, with an 18.7% increase compared to 2011, and an increase of daily doses (DDs) per 1,000 habitants of 8.6%, corresponding to a figure of 0.28.

Some orphan medicinal products can only be dispensed if the details of the patient are entered into the National Registry of Orphan Drugs, containing information on diagnosis and follow-up of the patient³⁰⁰.

Other initiatives to improve access to orphan medicinal products

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96³⁰¹ (a list of eligible drugs is annexed to this law). The Technical Committee of AIFA can include a given medication in the official list allowing it to be prescribed at the NHS charge, if for a specific disease there is no therapeutic choice. Three types of medical products can be included: innovative drugs for which the sale is authorised abroad, but not in Italy; drugs which have not yet received an authorisation, but have undergone clinical trials; and drugs to be used for a therapeutic indication different from the one which had been authorised³⁰². A Ministerial Decree of 8 May 2003³⁰³ allows for the prescription (paid by the producer) of drugs not yet authorised, but subjected to phase II or III clinical trials for the same therapeutic indication, for which a favourable evaluation in terms of efficacy and safety is expected.

The off-label use of a drug at the expense of NHS is allowed and provided to hospitalised patients, as envisaged by article 3, paragraph 2 of Law Decree³⁰⁴ 23/1998, when decided by a doctor on condition that this decision is made on a named patient basis, documented evidence is provided, and no other treatment is available. Medicines with non-approved indications are supplied through the “fondo AIFA 5%”.

The Ministerial Decree 11/2/1997 allows the import of unauthorised orphan medicinal products on a patient basis: in this instance, the payer is the Region or the NHS, in the case of hospital or reference centre use³⁰⁵.

At the end of 2010, an agreement between central Government and the Regions has established that ‘potential/important therapeutic innovations’ are automatically included on the regional formularies, so they should be available simultaneously and quickly across Italy¹⁵.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Respite care services, including “respite interventions” for families, either in residential or semi-residential structures, are included among the national LEA services and are mainly provided by governmental or accredited institutions, but are unevenly distributed within Italy and sometimes are provided by the private sector: full or partial reimbursement is offered and some patient organisations provide services free of charge.

³⁰⁰ Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Access Issues, Donald Macarthur (2011) p.83

³⁰¹ Law 23-12-1996 n. 648. Conversione in legge del D.L. 21 October 1996, n. 536, recante misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996 (published in GU 23 December 1996, n. 300).

³⁰² KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 p.50.

³⁰³ Ministerial Decree 8 May 2003 *Uso terapeutico di medicinale sottoposto a sperimentazione clinica* (published in GU 28 July 2003, n. 173).

³⁰⁴ Law Decree 17-2-1998 n. 23 Disposizioni urgenti in materia di sperimentazioni cliniche in campo oncologico e altre misure in materia sanitaria. (published in GU 17 February 1998, n. 39).

³⁰⁵ EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl, F. Bachner (2011) p54.

²¹ Istat 2008: *Gli interventi e i servizi sociali dei comuni singoli e associati*.

http://www3.istat.it/salastampa/comunicati/non_calendario/20110419_00/testointegrale20110419.pdf

Lodging, meals and other housing services are to be paid for by patients, or by municipalities, in the case of low-income situations.

Therapeutic recreational programmes are provided, although unevenly, by local authorities' social services under the administration of the municipalities. The institutional framework is complex: at governmental level, this competence belongs to the Ministry of Social Affairs, but the legislative power in terms of social policies is under the exclusive responsibility of Regions (Constitutional Law no. 3 October 18, 2001). It is the competence of the State to determine the essential level of benefits relating to civil and social rights that must be guaranteed throughout the national territory; the municipalities are the holders of administrative functions relating to social interventions undertaken at local level (Law n.328 November 8, 2000). Some municipalities assure public services, but more often services are run by private bodies (companies or patient organisations) commissioned by social authorities.

Some summer camps are informally or formally organised by patient organisations (e.g. the Dynamo Camp in Tuscany). These services are sometimes fully reimbursed, or there is a partial contribution according to the family income.

Additional social and/or financial support is available for families and patients with disabilities (Law Decree n. 509, 23 November 1988). Services promoting social integration of patients with disabilities in schools and the workplace are provided by the Government. The provision of specialised social services is thus unevenly distributed at national level. The average per-capita social spending of municipalities varies from €30 to €250²¹, and it is not considered satisfactory because the rules of access to services and the sharing costs are different in Regions. Furthermore there is a reduction in available resources: in years 2008-2011 there was a 89% cut of the National Welfare Fund, down from €1 billion 200 million to €69 million, only covered in part by Regions and municipalities.

1.15. LATVIA

Definition of a rare disease

Stakeholders in Latvia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals and that rare diseases are life-threatening or chronically debilitating diseases.

National plan/strategy for rare diseases and related actions

Work has recently been finished on a national plan by the working group, which included health care specialists and representatives from the Ministry of Health. In December 2011, the plan was written and submitted to the Ministry of Health for evaluation. The costs related to rare diseases are currently included in the national health care budget. A public consultation of the plan was launched in 2012 and the results were analysed by the Ministry of Health. A number of meetings with different stakeholders were held, and as a result, the plan was further elaborated. The plan should be able to be adopted in 2013.

A National Cancer Control Programme (2009-2015) was stipulated by regulations No.48 of the Cabinet of Ministers of the Republic of Latvia (adopted on the 29 January, 2009), and included rare cancers. In August 2009, a regulation was introduced which allowed for the compensation of medicines for children with rare diseases.

Centres of expertise

There are currently no official designated centres of expertise for rare diseases in Latvia, but, for example, the Latvian State University Children's Hospital provides genetics services, hospital specialists deal with children with haematological, oncological and endocrinological diseases. The Riga East University Hospital has a specialised clinic (Chemotherapy and haematology clinic) in which haemophilia A, haemophilia B, Factor XII deficiency and von Willebrand disease receive diagnostics and treatment (in this hospital, rare oncological diseases also can be treated, e.g. Burkitt's lymphoma, Langerhans cell histiocytosis, Mantle-cell NHL, multiple endocrinology neoplasia, Erwing's sarcoma, Wilm's tumour, Waldenström macroglobulinemia and others). Pauls Stradins University hospital has services in different rare diseases area: cardiology, nephrology, vascular diseases (Arteriovenous vascular malformations, lymphatic disorders, aortic pathology, endarteritis, carotid

tumors, etc.), ophthalmology, oncology, gastroenterology, endocrinology, pulmonology. A rare cardiovascular diseases network (Poland, Lithuania and Latvia through the P. Stradins Clinical University Hospital, Centre of Cardiology), started in May 2011. This project will last until January 2013.

The Ministry of Health, Orphanet team and experts from 3 University hospitals have been started work on developing national criteria for centres of expertise to be registered in Orphanet database.

Registries

There is no separate registry for rare diseases. The Centre for Disease Prevention and Control is the supervising authority and keeper of Register of patients with particular diseases, including cancers, congenital anomalies (some of these are rare diseases). There is a plan to pilot use the Orpha code for rare diseases in the register of patients with congenital anomalies. Latvia contributes to the EUROCARE (Eurocare-5 study) European registry, RARECARENet, Joint Action EUROCAT

Specialists from university hospital centres collect rare disease patient data, for example, at the Latvian Cardiology Centre is Pulmonary Arterial Hypertension patient's data base.

Neonatal screening policy

In Latvia, newborns are screened for phenylketonuria and congenital hypothyroidism. All activities connected with the evaluation of these tests and quality control are carried out by the Center for Disease Control and Prevention and under the supervision of the International Society of Neonatal Screening.

Genetic testing

Genetic testing is available in Medical Genetics Clinic of Latvian State University Children's Hospital, Molecular Laboratory, Riga Stradins University, Scientific Laboratory and in Latvian BioMedical Research and Study Center. No national guidelines and specific conditions for reimbursement of expenses related to the tests have yet been determined. Genetic testing in other EU and EFTA states is possible with a E112/S2 form if genetic testing is a health care service usually financed from the state budget and this service cannot be provided in the Republic of Latvia or cannot be provided within a reasonable period of time.

Diagnostic tests are registered as available in Latvia for 10 genes and an estimated 9 diseases in the Orphanet database³⁰⁶.

National alliances of patient organisations and patient representation

In 2009 the Latvian Rare Disease Organisation Caladrius³⁰⁷ was launched. The mission of the organisation is to provide patients with the relevant information and support and to represent patients. In 2010 Caladrius established a fund to help rare disease patients who could not otherwise fund their treatments: the organisation had obtained public benefit organisation status to legally collect funds for this action. There are plans to create an alliance of rare diseases patient organisations and chronic patient organisations at national level. Until now there were 8-9 organisations who share information and collaborate together in this area. Rare diseases patient organisations lack the capacity to establish an alliance.

In Latvia are a number of other rare diseases and rare diseases-related patient organisations, including the Haemophilia Society, the Society for People with Disabilities Motus Vitae, the Phenylketonuria Society, Pulmonary Hypertension Society and Society of Cystic fibrosis. These organisations often collaborate with each other and in 2011 had many activities, for example, Motus Vitae joined the International ALS/MND Alliance and arranged the international conference VII Nordic ALS Alliance meeting in Latvia "Baltic Bridge": Services for people living with ALS/MND (there participated patients with their assistants, medical professionals, social workers and Health Care Institutions from Denmark, Finland, Estonia, Russia, Iceland and Latvia).

Palidzesim.lv is a non-governmental organisation which financially supports children and families to confirm a diagnosis of rare diseases by sending patients or medical samples abroad³⁰⁸.

³⁰⁶ Information extracted from the Orphanet database (December 2012).

³⁰⁷ www.caladrius.lv

Sources of information on rare diseases and national help lines

Orphanet activities in Latvia

The Ministry of Health of the Republic of Latvia has designated The Centre for Disease Prevention and Control as the representative of the Republic of Latvia to participate in the Joint Action Orphanet Europe since April 2012. The Orphanet team is currently hosted by the Centre for Disease Prevention and Control and is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Latvia for entry into the Orphanet database. The Orphanet Latvia country site was launched in April 2012 and regularly updated by the Orphanet team.

Official information centre on rare diseases

There is no information centre for rare diseases in Latvia other than Orphanet. Web based information is available for a limited number of diseases (rare and non-rare) and certain information is maintained by using the state budget.

Help line

There are non-rare disease specific help lines run by the state, some by the state budget, to help patients to access health care and psychological support, but no help line dedicated to rare diseases.

Other sources of information on rare diseases

Information on rare diseases is available regarding paediatric rheumatic diseases³⁰⁹, lysosomal diseases (Gaucher disease, Fabry disease and Hunter syndrome)³¹⁰, pulmonary hypertension³¹¹, bleeding disorders³¹², and via PHL Latvia³¹³.

Good practice guidelines

No best practice guidelines for rare diseases have been produced at national level in 2012.

Training and education initiatives

No events reported yet.

National rare disease events in 2012

The Rare Disease Association Caladrius, Latvian Association of Hemophilia, PHA Latvia and the Association Motus Vita all marked Rare Disease Day in Latvia on 29 February 2012 with an event entitled 'SOLIDARITY'. The event took place in the EU House Conference Hall in Riga. The event served to highlight a number of issues concerning the quality of care for rare disease patients, as well as access to diagnosis and treatment, and aimed to make suggestions concerning what can be done to improve the situation for rare disease patients in Latvia. The Children's Hospital organised a day to raise awareness of cystic fibrosis dedicated to the parents and primary care providers.

Hosted rare disease events in 2012

No hosted events were reported.

Research activities and E-Rare partnership

National research activities

Funding is available for rare disease projects (through state budget, charities and pharmaceutical companies) although funds are not specifically earmarked for rare disease research.

Participation in European research projects

A Latvian team participates in the European Haemophilia Safety Surveillance- EUHASS European research project.

³⁰⁹ <http://www.printo.it/pediatric-rheumatology/information/Lettonia/index.htm>

³¹⁰ <http://lus.dev.zvirbulis.lv/lv/sakums>

³¹¹ <http://lus.dev.zvirbulis.lv/lv/sakums>

³¹² www.hemofilija.lv

³¹³ www.phlatvia.lv

E-Rare

Latvia is not currently a partner of the E-Rare project.

IRDiRC

Latvian funding agencies do not currently contribute funds to the IRDiRC.

Orphan medicinal products

The State Agency of Medicines of Latvia is responsible for regular collecting and distributing of the information on medicines, including orphan medicinal products, as well as for collecting and compiling the information on the safety, evaluating drug risks and coordinate measures of medicine use risk mitigation, according to Regulations No. 1006 of the Cabinet of Ministers (adopted on December 7, 2004) "State Agency of Medicines Statutes".

Orphan medicinal product committee

A representative of Latvia is a member of the Committee for Orphan Medicinal Products (COMP) of European Medicines Agency.

Orphan medicinal product incentives

The *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* reported that in Latvia "the State Agency of Medicines is entitled, due to considerations of health protection, to make a decision (after discussion with the Minister for Health) regarding the fee exemption or reduction for activities associated with the evaluation, registration or re-registration of a medicinal product if the medicinal product (with or without orphan designation pursuant to Regulation 141/2000) is intended to the treatment of a rare disease."³¹⁴

Under the centralised procedure, companies submit a single marketing-authorisation application to the European Medicines Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation for Orphan medicinal products is valid in all European Union (including Latvia) and EEA-EFTA states.

Orphan medicinal product market availability situation

The State Agency of Medicines of Latvia's includes the medicinal products registered in the Republic of Latvia and the centrally registered medicinal products (including orphan medicinal products) in a register³¹⁵ of medical products of the Republic of Latvia (according to Regulations No. 376 of the Cabinet of Ministers (adopted on May 9, 2006) "Procedures for the Registration of Medicinal Products").

The following orphan medicinal products were marketed in Latvia in 2012: Aldurazyme, Cystadane, Diacomit, Gliolan, INCRELEX, Jakavi, Kuvan, Litak, Mozobil, Myrin, Nexavar, Pedeia, Revatio, Sprycel, Tasigna, Ventavis, Volibris, Wilzin, Yondelis. In 2012, compared to 2011, 3 new orphan drugs were launched on the market: Aldurazyme, Jakavi, Yondelis and 3 orphan drugs were no longer available on the market in 2012: Arzerra, Nplate, Revolade. Medicinal product Glivec which was originally designated as an orphan medicine and was placed on the market in 2011 is no longer designated as an orphan drug in Europe

Orphan medicinal product pricing policy

There are no specific provisions for the pricing of orphan drugs. There have not been any developments in this area

Orphan medicinal product reimbursement policy

Since 2009, some orphan medicinal products for children are available as a part of the special programme "Medical treatment of rare diseases for children" for Children's University Hospital, Riga. Within this programme, there are provided some orphan medicinal products like Elaprase, Cystadane, Increlex, Kuvan.

Orphan medicinal products are partially available via the reimbursement system. Imatinibum, Dasatinibum, Nilotinibum are included in the positive reimbursement list.

³¹⁴ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp16-17)

³¹⁵ <http://www.zva.gov.lv/index.php?id=112&top=112&large=>

2% of reimbursement budget is intended to individual reimbursement with limitation up to 10 000 LVL/year for a single patient. Within this individual reimbursement, the following orphan medicinal products are provided: Revatio, Volibris, Nexavar, Cystadane, Diacomit, Mozobil, Thalidomide.

Other initiatives to improve the availability of orphan medicinal products

The *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* reported that in Latvia "The State Agency of Medicines may issue [...] distribution authorisation for medicinal products not registered in Latvia if the medicinal product is intended for treatment of a rare disease (for an individual patient on the basis of prescription or for use in a health care institution on the basis of a written request)."³¹⁶

Orphan devices

There were no orphan devices placed on the market in 2012

Other therapies for rare diseases

No specific information reported.

Specialised social services

Respite care services are available and the categories of patients eligible for reimbursement are described in the "Procedures for the Organisation and Financing of Health Care" (Regulations of the Cabinet of Ministers No. 1046, adopted on 19 December 2006). Therapeutic recreational programmes are also available and costs are included in the national health care budget. There are existing government-run services promoting social integration of those with handicaps, including the school environment and work place.

1.16. LITHUANIA

Definition of a rare disease

Stakeholders in Lithuania accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

On 18 October 2012, the national plan for rare diseases was approved by the Order No V-938 of the Minister of Health, and a national rare diseases coordination committee was formed, including delegated experts from university hospitals, universities, non-governmental organizations, state institutions representatives to oversee the plan. The plan aims to establish a common approach on rare diseases, to raise public awareness, and to ensure prevention, early diagnosis, efficient treatment, improvement of quality of life and social support for patients suffering from rare diseases. It also includes the optimisation of health care services and rational allocation of available resources, as well as measures for improving the assessment of medicinal products and medical devices.

Expenses for health care services and drugs for rare diseases patients are reimbursed from the Compulsory Health Insurance Fund budget as for other groups of patients, e. g. are not separated from total Compulsory Health Insurance Fund except specific allocations for reimbursement of rare medicinal products and devices. Additionally, expenses for the treatment of rare cases abroad are reimbursed from Compulsory Health Insurance Fund budget; compensation for orphan medicinal products and medicinal devices for rare diseases and conditions are paid from a selected part of the budget of the Compulsory Health Insurance Fund (Order No. 151 of 20 March 1998 of the Ministry of Health). In 2012 12,97 million litas (about 3,6 million of euro) were allocated to reimbursing rare medicinal products and devices.

Centres of expertise

There are no official centres of expertise in Lithuania, but two centres (Centre for Medical Genetics in Vilnius University Hospital Santariškių Clinics and the Hospital of Kaunas University of Medicine) provide genetics

³¹⁶ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (pp16-17)

services and diagnostic services for rare diseases to the Lithuanian population. A specialist group has been created, at the Centre for Medical Genetics at Vilnius University Hospital Santariškių Klinikos, for the creation of rare diseases management plans and a rare diseases registry and an expert centre for diagnosis, treatment and management of rare diseases was established there in November 2012. An outpatient clinic for cystic fibrosis patients was established in 2011. A coordination centre for children with rare diseases has been established at Vilnius Children's Hospital³¹⁷.

Registries

A specialist group has been created, at the Centre for Medical Genetics at Vilnius University Hospital Santariškių Klinikos, for the creation of a rare diseases registry.

Under the Law of National Information resources the establishment of National Registry can be founded on the legal background only.

Establishment of various diseases is quite long and costly process, this is why Lithuania is looking to innovate by establishing electronic, platform-based registries during the period of implementation of E-Health project 2013-2015. Registries of separate diseases (rare included) will function as subsystem of National E-Health information system and will be integrated into common data network.

Lithuania contributes to the EURO CARE CF registry.

Neonatal screening policy

Newborn screening programmes are in place for phenylketonuria and hypothyroidism (Order No. V-865 of the Minister of Health of Republic of Lithuania of 6 December 2004 "Regarding the Approval of Universal Screening of Newborns for Inborn Metabolism Disorders Procedures").

The basic prices paid from Compulsory Health Insurance Fund budget for the newborn screening programmes for phenylketonuria and hypothyroidism were re-counted and approved by the Order No. V-962 of the Minister of Health of Republic of Lithuania in 10 November 2011.

An Order of the Minister of Health (2012-05-28 No V-470) in 2012 approved obligatory screening of newborns' vision.

Genetic testing

Genetic testing is provided for patients of high risk group according to Ministry of Health Decree Nr.V-522 of 23 June 2005; the expenses related to this testing are reimbursed from Compulsory Health Insurance Fund budget.

Diagnostic tests are registered as available in Lithuania for 36 genes and an estimated 14 diseases in the Orphanet database³¹⁸.

Genetic testing is available in two main University Hospitals and several private laboratories. Only the clinical geneticist can order the genetic testing at academic hospitals, as established in Order of Minister of Health 2012-08-02 No. V-745).

There are no reference genetic laboratories in Lithuania, and different laboratories use self-prepared guidelines/protocols.

Basic prices for reimbursement of genetic testing are approved Order of Minister of Health 2011-11-10 No. V-962) Genetic testing abroad is reimbursed on referral by the University Hospital's consilium and decision of Commission at the Ministry of Health are needed) as established in Order of Minister of Health 2010-08-16 No. V-729.

National alliances of patient organisations and patient representation

Although there is no alliance of rare disease patient organisations In Lithuania, a Council of Representatives of Lithuanian Patient Organisations is in place which brings together about 20 different non-governmental patient organisations (including rare disease) and seeks to achieve common goals and rights. There are several separate patient organisations for patients with rare diseases, including phenylketonuria, rare oncological diseases, Alpha-1-antitrypsin insufficiency disease, haemophilia, patients with impaired hearing, cystic fibrosis. There is a general Alliance of Patient Organisations in Lithuania, covering rare diseases patient organisations as well³¹⁹.

³¹⁷ <http://www.vaikuligonine.lt>

³¹⁸ Information extracted from the Orphanet database (December 2012).

³¹⁹ <http://www.pacienturyba.lt>

Patient organisations receive funding mainly from private sponsorship, donations and income tax donations. Patient organisations are represented at the Compulsory Health Insurance Council, and at the Council of Representatives of Patient Organisations under the Ministry of Healthcare. Members of patient organisations are involved into working groups organised by orders of the Health Ministry, Parliament, and the representatives of patient organisations also participate in the Patient's Rights and Damage for Health Compensation Commission at the Health Ministry. Members of patient organisations will be involved in elaborating the national plan for rare diseases as well.

Sources of information on rare diseases and national help lines

Orphanet activities in Lithuania

Since 2004 there is a dedicated Orphanet team in Lithuania, currently hosted by the Department of Human and Medical Genetics at the University of Vilnius. The Ministry of Health designated this team as the official Orphanet team for Lithuania in 2010 in the context of the Orphanet Europe Joint Action. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Lithuania³²⁰ national website in Lithuanian.

Official information centre on rare diseases

The only official common information source on rare diseases in Lithuania is Orphanet.

Helpline

There is currently no help line dedicated to providing information on rare diseases, but other general help lines (e.g. providing psychological support) exist.

Other sources of information on rare diseases

The website of Coordinating Center on Rare Diseases at the University Children's Hospital at the Vilnius University Hospital Santariskiu Klinikos provides web-based information³²¹.

Lithuania is a partner in the ECORN-CF project which maintains a website and forum for patients with cystic fibrosis, their relatives and any other interested parties where they can ask questions and obtain answers from experts. Although the EC-funding of this project has ended, the service continues to be sustained through other sources of financing.

Good practice guidelines

A "National agreement for cystic fibrosis diagnostic and treatment: evidence based methodical recommendations"³²² was published in the journal *Paediatric pulmonology and allergology* (Vol. XIII, Nr. 2): this agreement was reached in October 2010 between paediatricians and pulmonologists and concerns best practice for cystic fibrosis treatment.

A national agreement for cystic fibrosis diagnostic, treatment and management for adults was reached and published in journal *Pulmonology, immunology and allergology* (1(8), 2011)

Training and education initiatives

A training program for the improvement in rare diseases diagnostics for doctors has been initiated and a training cycle called "Rare diseases" has been introduced for medical students.

National rare disease events in 2012

A press conference was held on 28 February 2012 to mark Rare Disease Day 2012: this event was organised by the Lithuanian Society of Human Genetics. On 29 February 2012, a conference entitled "Rare children's diseases: problems and decisions" was held Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, to mark Rare Disease Day 2012. A number of press releases and informative documents were provided by the Ministry of Health on the day (e.g. the Ministry of Health of Republic of Lithuania published an annual press release on the policy on rare diseases; the calendar of the Ministry of Health marked 29 of February as Rare Disease Day).

³²⁰ <http://www.orpha.net/national/LT-LT>

³²¹ http://www.vaikuligone.lt/centras.php?cen_id=16

³²² <http://www.pediatrija.org>

A conference on rare diseases was also organised on 28 September 2012 to mark the 75th anniversary of the Paediatrics Society of Lithuania. The event was supported by the European Academy of Paediatrics, and the conference was attended by its President, as well as foreign representatives, geneticists, paediatric surgeons, family doctors and other physicians.

Hosted rare disease events in 2012

No specific activity reported.

Research activities and E-Rare partnership

National research activities

In the recent years funding is available for fundamental research and research concerning medicinal products: this second area of research is in particular targeted by the European Union Structural Assistance Operational Programme 2007-2017 for Economical Growth and research projects for rare diseases may receive financial support by taking part in tendering processes. Additionally, in 2007 the Government of the Republic of Lithuania adopted the Lithuanian Research and Development Priorities for 2007-2010 (Governmental Decree No. 166, 7 February 2007) which also includes as a priority the development of medicinal products, including those targeting rare diseases.

An academic research project in Lithuania entitled "National hereditary childhood cancer research platform" which focuses on six genetic diseases (von Hippel-Lindau syndrome, Li-Fraumeni syndrome, Multiple endocrine neoplasia syndromes - MEN1 and MEN2, Familial adenomatous polyposis and Type 2 Neurofibromatosis), molecular epidemiology and establishing of molecular diagnostic facility as well as information dissemination concerning rare diseases is on-going.

Participation in European research projects

Lithuanian teams participate, or have participated, in the EUROPEAN LEUKEMIA NET and IMPACTT research projects.

E-Rare

Lithuania is not currently part of the E-Rare consortium.

IRDiRC

Lithuanian funding agencies do not currently contribute funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

A committee, set up by the Health Ministry's State Patient Fund, responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions. Lithuania as an EU MS has a national representative at the COMP.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

Orphan medicinal products are available in the same way as the medicines authorised in all EU states. The website of the Lithuanian State Medicines Control Agency³²³ provides information including the list of authorised medicines but does not give any other information concerning orphan medicinal products apart from that provided by the EMA concerning orphan medicinal products with EU market authorisations.

29 centrally authorised products were marketed in Lithuania in 2011. These include Arzerra (ofatumumab), Atriance (nelarabine), Busilvex (busulfan), Evoltra (clofirabine), Fabrazyme (agalsidase beta), Gliolan (5-aminolevulinic acid hydrochloride), Glivec (imatinib), Increlex (mecasermin), Inovelon (rufinamide), Litak (cladribine), Lydodren (mitotane), Mozobil (plerixafor), Nexavar (sorafenib), Orfadin (nitisinone), Pedeia (ibuprofen), Revatio (sildenafil), Rvlimid (lenalidomide), Revolade (eltrombopag), Sprecel (dasatinib), Tassigna (nilotinib), Tepadina (thiotepa), Thalidomide Celgene (thalidomide), Torisel (temsirolimus), Tracleer (bosentan monohydrate), Trisenox (arsenic trioxide), Ventavis (iloprost), Volibris (ambrisentan), Wilzin (zinc), Yondelis (trabectedin). The majority of these medicines were marketed, other were available on patient basis. In

³²³ <http://www.vvkt.lt/>

addition, nationally authorised anagrelide (Thromboreductin) and inhaled tobramycin (Tobramycin Norameda) were available in 2011.

Orphan medicinal product pricing policy

No specific activity reported.

Orphan medicinal product reimbursement policy

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*³²⁴ concerning Lithuania, "compensation for orphan medicinal products and medicinal products for rare diseases and conditions is paid for out of the funds earmarked for that purpose in the budget of the compulsory health insurance fund (Ministry of Health Decree No 151 of 20 March 1998; Official Gazette, 1998, No 33-894; 1999, No 7-159). A list of reimbursed medical products is available (the last update is dated 2 February 2009, Ministry of Health Decree No V-52, regarding the amendment of Order No.49 of 28 January 2000 "Regarding the Approval of the List of Reimbursed Medicinal Products"). Individuals are compensated for the purchase of medicinal products for rare diseases and conditions on presentation of specialist doctors' reports, following a decision by the committee, set up by the the National Health Insurance Fund under the Ministry of Health, responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions and on cases for which no provision has been made (Decree of the Director of the National Health Insurance Fund under the Ministry of Health No 1K-149 of 22 November 2005; Official Gazette, 2005, No 139-5037)."

Other initiatives to improve access to orphan medicinal products

No specific activity reported.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

The Committee at the *National Health Insurance Fund under the Ministry of Health* responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions also makes decisions on compensation of orthopaedic hardware in rare diseases and conditions.

Specialised social services

Respite care services are available and are organised by municipalities and hospital clinics: the Kaunas Children's Development Clinic, the Centre of Children's Development at Vilnius University Children's Hospital and day care centres for mentally disabled patients at municipal level. Therapeutic recreational programmes are available and are provided by local authorities under the administration of municipalities and directed at government level by the Ministry of Social Security and Labour. Some municipalities provide public services but these services are mostly run by private bodies (either companies or patient groups) commissioned by the social authorities. Educational camps are available for children, organised by the Ministry of Education. Rehabilitation issues are regulated by Healthcare Ministerial Order No. V-50 (17 January 2008) "Regarding the Organisation of Medical Rehabilitation and Sanatorium". Governmental services are available to promote social integration including integration in schools and the work place of patients with disabilities: this includes personalised secondary training syllabi and a special integration programme for sick and disabled persons for the labour market.

A recreational camp for haemophilia patients and their family members entitled "Barger 2012" took place in May 2012.

³²⁴ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p17)

1.17. LUXEMBOURG

Definition of a rare disease

Stakeholders in Luxembourg accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

The Task Force on Rare Diseases Luxembourg ("*Groupe de travail maladies rares*") was created in 2005 to analyse the needs of rare disease patients in the country and to develop a national strategy for improvement. This Task Force is working on a national plan for rare diseases based on the results of a survey ("*Rare diseases: a national survey on the situation of persons with rare diseases in Luxembourg*³²⁵") carried out between May 2006 and February 2007 aimed at analysing the strengths and weaknesses of the healthcare system and the experiences of rare disease patients. The results of this survey were published on 28 February 2011³²⁶. The results of the survey show that, as in many other European countries, obtaining a diagnosis is often difficult for rare diseases patients in Luxembourg; that medical and scientific knowledge is often insufficient, as Luxembourg does not have university hospitals or specialised investigation centres; that often there is a lack of information on diseases or specialised treatment centres abroad. Whereas the orientation of patients to a specialist or a specialised centre abroad (when these are identified) is a procedure foreseen in the national sickness fund, patients regret an lack of coordination between the health professionals; there is a lack of quality care for quite a number of rare pathologies; as parts of the care and treatment might not be covered by the sickness fund there are inequalities in the access to a diagnosis, treatments and care; and that rare diseases have serious social consequences. A list of recommendations have been made on the basis of these results including: the elaboration of a national plan for rare diseases; the improvement of information and awareness of rare diseases; the guarantee of equal access to diagnosis, care and treatment; the provision of specific help services for patients with rare diseases and their families; to the support of rare disease patient organisations and their involvement in national rare disease actions; to intensification of international collaboration; the promotion of advanced research; and the support for the sustainability of rare disease initiatives at national level.

According to the results of the survey, 95% of patients with rare diseases residing in Luxembourg have sought or have been oriented by their treating doctor for medical care in neighbouring countries (such as Germany, Belgium and France), with 50% of patients travelling 1 to 5 times a year abroad for medical care.

Concertation on a plan was reinforced at Ministry level in 2012.

Centres of expertise

There are currently no official centres of expertise for rare diseases in Luxembourg. However a new system for referrals has recently been introduced which should improve access to healthcare.

Registries

Luxembourg contributes to the EURO CARE CF European registry.

Neonatal screening policy

A national neonatal screening programme is in place for phenylketonuria (since 1968), congenital hyperthyroidism (since 1978), congenital adrenal hyperplasia (since 2001) and Medium-Chain Acyl-CoA Deficiency (since 2008).

Genetic testing

No specific information reported.

National alliances of patient organisations and patient representation

The Luxembourg Association for Neuromuscular and Rare Disorders (ALAN absl.) was established in 1998 to represent patients with neuromuscular diseases: since 2006 they have provided support for other rare disease patients for whom there is no other patient organisations. The association organises informative events, counselling, guidance and self-help groups and is involved in the work of the Task Force on Rare Diseases

³²⁶ *Les maladies rares: Enquête sur la situation des personnes atteintes de maladies rares au Grand-Duché de Luxembourg*
<http://www.sante.public.lu/fr/catalogue-publications/maladies-traitements/maladies-rares/index.html>

Luxembourg. There are other patient organisations for single or groups of rare diseases. There is the intention to create an alliance of rare disease patient organisations.

Sources of information on rare diseases and national help lines

Orphanet activities in Luxembourg

Since 2006, there is a dedicated Orphanet team in Luxembourg, currently hosted by the Ministry of Health. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Luxembourg for entry into the Orphanet database.

Official information centre for rare diseases

The Task Force has plans to soon put into place a national rare diseases platform which offers medical and social services, a rare disease hotline, counselling, self-help groups, specialised information on rare diseases and guidelines of best practices. A guide to all medical, paramedical and social services available to rare disease patients and their family should also be made available online.

Help line

A rare disease help line is one of the activities to be hosted by the national rare diseases platform.

Other sources of information on rare diseases

No specific information reported.

Good practice guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

National rare disease events in 2012

To mark Rare Disease Day 2012, a week of awareness-raising activities were organised by ALAN absl from 22 to 29 February 2012 at the Belle Etoile shopping centre: this event included a photo exhibition including photos of people with rare diseases posing next to celebrities from Luxembourg. A number of personalities participated, including the Deputy and Bourgmestre of the town of Luxembourg Mr. Bettel.

Hosted rare disease events in 2012

No hosted events were reported in 2012.

Research activities and E-Rare partnership

National research activities

An annual rare disease telethon, organised by the Lions Club, raises money and pools this with that of the AFM (*Association française contre les myopathies*) which then redistributes these funds to research projects, including some in Luxembourg.

Participation in European research projects

Luxembourg does not currently participate, or has not participated, in any European research projects for rare diseases.

E-Rare

Luxembourg is not currently a partner of the E-Rare project.

IRDiRC

Funding agencies from Luxembourg have not yet committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

The Task Force aims to create a national medical commission to consult on issues regarding access to and reimbursement of orphan medicinal products.

Orphan medicinal product incentives

No specific information reported.

Orphan medicinal product market availability situation

The orphan medicinal product/medicines for rare diseases available in Luxembourg are³²⁷: Carbaglu, Cystadane, Naglazyme, Replagal, Fabrazyme, Aldurazyme, Myozyme, Elaprase, Vpriv, Orfadin, Wilzin, Zavesca, Kuvan, Revestive, Novo Thirteen, Nplate, Revolade, Firazyf, Redea, Tracleer, Volibris, Glybera, Revatio, Increlex, Somavert, Plenadren, Cayston, Tobi Podhaler, Busilvex, Tepadina, Mercaptopurine, Litak, Atriance, Vidaza, Dacogen, Yondelis, Arzerra, Adcetris, Photobarr, Gliolan, Nexavar, Sprycel, Tassigna, Torisel, Votubia, Jakavi, Siklos, Lysodren, Trisenox, Xagrid, Ceplene, Mepact, Mozobil, Soliris, Arcalyst, Ilaris, Tacni-1, Esbriet, Thalidomide Pharmion, Revlimid, Prialt, Inovelon, Diacomit, Duodopa, Nymusa, Vyndaqel, Firdapse, Bronchitol, Kalydeco, Exjade and Savene.

Orphan medicinal product pricing policy

No specific information reported.

Orphan medicinal product reimbursement policy

No specific information reported.

Other initiatives to improve access to orphan medicinal products

No specific information reported.

Orphan devices

No specific information reported.

Other therapies for rare diseases

No specific information reported.

Specialised social services

No specific information reported.

1.18. MALTA



Definition of a rare disease

Stakeholders in Malta accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

There is currently no national plan/strategy for rare diseases in place in Malta. A Task Force for the implementation of the key requirements for Member States for the Council Recommendations on a European action in the field of rare diseases was set up in October 2010. An advanced first draft of the National Plan on Rare Diseases was completed in 2012. An internal consultation exercise was also completed. A public consultation on the plan will take place in 2013. The national strategy will have a time span of a number of years with plans to incrementally implement a number of measures that will aim towards increasing the profile and care services tailored for rare diseases in Malta.

Centres of expertise

There are currently no official reference centres of expertise for rare diseases in Malta (see "Pilot European Reference Networks"). Assistance by local government for treatment abroad (namely in the UK) is possible

³²⁷ As of April 2013.

through a bilateral health agreement between the two countries. Further agreements with other EU Member States are being sought, developed and completed. For example, since 2012 Malta is sending patients to centres in Italy for specialised investigation and treatment such as lung transplants. There is only one potential centre of expertise (and indeed also one referral centre) which comprises the major acute general hospital; Mater Dei Hospital. This hospital caters for the majority of the secondary and tertiary healthcare provision in Malta. It is a teaching hospital (in conjunction with the University of Malta) and it is a public hospital. In addition, from 2014 onwards it is also planned to house the new Oncology Hospital which is currently under construction on the Mater Dei Hospital site.

Registries

There is currently no system for the designation of registries for rare diseases in Malta. However work has been done on the possible sources of data on rare disease patients in order to assess feasibility for future steps. Malta contributes to the EUROCAT European registry as well as the RARECARE and EUROCAT projects through the Malta National Cancer Registry. It is also participating in EPIRARE and PARENT projects.

Neonatal screening policy

Neonatal screening is available for haemoglobinopathies and hypothyroidism.

Genetic testing

Genetic studies (karyotyping and molecular genetic studies) in foetuses and neonates born with congenital malformations or rare syndromes are available. There are 3 consultant geneticists and 2 genetics laboratories in Malta, the Molecular Genetics Laboratory and Cytogenetics Laboratory. The indicated genetic tests that are not performed in house are referred to a reference laboratory/centre abroad. The funding for these tests is covered by the local health authorities.

National alliances of patient organisations and patient representation

Malta does not currently have an official national alliance of rare diseases patient organisations.

Sources of information on rare diseases and national help lines

Orphanet activities in Malta

The government of Malta has not designated a national Orphanet team for Malta to date.

Official information centre for rare diseases

There is no official information centre on rare diseases in Malta to date.

Help line

Although there is no official help line for rare diseases, the agency Sapport provides support by telephone to all disabled people that request it. This service is funded by the government.

Other sources of information on rare diseases

There were no further developments in the sources of information on rare diseases in 2012.

Good practice guidelines

No best practice guidelines for rare diseases have been produced at national level in 2012.

Training and education initiatives

There are currently no initiatives specifically dedicated to rare disease-specific training and education in Malta.

National rare disease events in 2012

In 2012 to mark Rare Disease Day, an expression of the solidarity event, in collaboration between the Malta Health Network and the Malta Health Authorities, was held at Mater Dei Hospital, on 29 February 2012.

Hosted rare disease events in 2012

No specific activity reported.

Research activities and E-Rare partnership

National research activities

Funding for research into haemoglobinopathies and other rare genetic disorders is available through various sources (including the European Structural Funds, Ithamet and the University of Malta).

Participation in European research projects

Teams from Malta are currently taking part in two EU-funded projects related to rare diseases. These are RD-Connect and BBMRI (Biobanking and Biomolecular Resources Research Infrastructure).

E-Rare

Malta is not currently a partner for the E-Rare project.

IRDiRC

Malta is not currently a partner in IRDiRC.

Orphan medicinal products

Since the start of 2010 Malta participated in the project “Assessing Drug Effectiveness” (an initiative of the Swedish Presidency) and is currently participating in the project “Mechanism of Coordinated Access to Orphan Medicinal Products” (an initiative of the Belgian Presidency). Malta is also participating in the BBMRI initiative of the EU.

Orphan medicinal product committee

Orphan medicinal products are registered through the centralised procedure and Malta has a member on the Committee for Orphan Medicinal Products and on the Committee for Human Medicinal Products of the European Medicines Agency.

Orphan medicinal product incentives

No specific reported activity.

Orphan medicinal product market availability situation

There is no information about the number of orphan medicinal products which are available on the private market. Information gathered by the Directorate of Pharmaceutical Affairs shows that only two orphan medicinal products are purchased and placed on the market and are not provided through the government system for free medicinals: Ecteinascidin 743 (Yondelis) and Sorafenib tosylate (Nexavar). In addition, 29 orphan medicinal products are available within the National Health Scheme (see below).

Orphan medicinal product pricing policy

With regards to reimbursement processes within the National Health Scheme, if an orphan medicinal product is approved through the Exceptional Medicines Treatment Policy, there will be no specific provisions for pricing. However, when a request for introduction into the Government Formulary List is submitted and approved, the pricing policy as for all other new medicines applies. The Pricing Policy for the National Health Scheme was launched in 2010.

Orphan medicinal product reimbursement policy

The Government Formulary List contains a number of orphan medicinal products which are reimbursed according to government entitlement policies. The Exceptional Medicines Treatment Policy allows for specific provisions for the reimbursement of orphan medicinal products, which are either not listed on the Government Formulary List or are not according to government policies.

The following orphan medicinal products are currently being reimbursed³²⁸: Amifampridine, Anagrelide, Azacitidine, Bosentan, Caffeine citrate, Celecoxib, Cinacalcet**, Cladribine, Clofarabine, Colistimethate sodium*³²⁹, Dasatinib, Deferasirox, Dornase alfa**, Eptacog Alfa (Recombinant Factor VIIa), Human Cytomegalovirus Immunoglobulin, Iloprost, Imatinib, Lenalidomide, Levamisol hydrochloride, Mercaptopurine liquid, N-Acetylcysteine*, Nilotinib, Nitazoxanide**, Oxaliplatin, Pegvisomant, Pemetrexed*, Plerixafor,

³²⁸ Source: Directorate of Pharmaceutical Affairs, Ministry for Health (10 April 2013)

³²⁹ * Drugs with non-EU orphan designation for rare diseases. ** Drugs for which EU orphan designation has been removed.

Rufinamide, Sildenafil, Stiripentol³³⁰, Sulfadiazine, Sunitinib*, Thalidomide, Thiotepa, Tiopronine**, Tobramycin (inhalation solution), Topotecan, Vigabatrin. The drugs available within the National Health Scheme are either on the national Government Formulary List or approved through the Exceptional Medicines Treatment Policy and are fully reimbursed and available for dispensing, free of expense to the patients entitled to them.

Other initiatives to improve access to orphan medicinal products

All medicinal products must be authorised before they can be marketed in the European Union. However, a treatment option for patients in the European Union suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may be the use of an unauthorised medicinal product in a compassionate use programme. Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

To obtain an authorisation in line with compassionate use, as per Article 83 of Regulation (EC) No 726/2004 on compassionate use, applicants submit a request to the Licensing Authority. The product being applied for under compassionate use needs to be specifically under evaluation in the centralised authorisation procedure at the European Medicines Agency.

Off-label use is the use of a product outside its licensed indications. Off-label use is possible at the responsibility of the prescribing physician.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

There are no specific initiatives in place concerning orphan devices in Malta. To date, Malta has retained the view that an EU regulation on orphan medical devices is neither necessary nor beneficial and that the current legal framework already caters for rare diseases.

Specialised social services

There are limited respite care services and there is an element of co-payment, as with all other residential long-term care services. Therapeutic recreational programmes are also available, and subsidies are available: these services are provided by not-for-profit organisations. There is close liaison between health and education authorities to support children in the mainstream schools for the implementation of inclusive education. This includes support to teachers to provide inclusive education at national level. A wide range of services by health care professionals are offered in the community by the health care division through Primary Health Care services such as speech language services and physiotherapy. In addition, there are also social security benefits for those with disabilities.

1.19. THE NETHERLANDS

Definition of a rare disease

Regulation (EC) 141/2000 on orphan medicinal products defines a rare disease: the prevalence of a rare disease is not higher than five per 10,000 individuals. The Netherlands will take no initiatives to amend the definition.

National plan/strategy for rare diseases and related actions

The Health insurance Act is at the basis of the Netherlands' health care system. All patients, including patients with a rare disease, are entitled to diagnosis, care and rehabilitation in line with this Act.

The Minister of Health, Welfare and Sport, Mrs. E. Schippers, sent a letter (with annex) to Parliament on 29 February 2012, in which she expounded the strategy of the Dutch government regarding rare diseases for the years 2012-2015. Some important points in this report are the following:

³³⁰ Request withdrawn therefore not reimbursed.

- Strengthening the role of university hospitals with regard to patient care and research in rare diseases (and centres of expertise);
- Funding (only university hospitals) is designated for care and research;
- Improving reimbursement of orphan medicinal products applied in university hospitals starting 1 January 2012 and in the out-patient setting (starting in 2013). This new policy will not hinder the accessibility of orphan medicinal products;
- The Steering Committee on Orphan Drugs was dissolved (as of 31 December 2011), but stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise;
- ZonMw (The Netherlands Organisation for Health Research and Development) assume tasks not taken up by the stakeholders that remain from the tasks of the former Steering Committee. The ministry of Health, Welfare and Sport provides funding for the years 2012-2015;
- The Forum Biotechnology and Genetics (also fully subsidised by the ministry of Health, Welfare and Sport) will assume more responsibility on rare diseases and orphan medicinal products;
- A statement on screening.

In addition to this strategy, preparations for a national plan on rare diseases for all stakeholders have started. The Netherlands Organisation for Health Research and Development (ZonMw), has been commissioned by the Ministry of Health, Welfare and Sport to coordinate the input for a National Plan following up on the initial work of the Dutch Steering Committee on Orphan Drugs.

The input of all stakeholders was collected via information from different meetings organised in the last year and via working groups and the website, coordinated by ZonMw/NPZZ and under the auspices of a sounding board especially formed for this task (<http://www.npzz.nl/>). The website will make public the preparatory documents for the National Plan. In January-March 2012, stakeholders started collecting possible solutions for the issues raised and discussing these on the website and in a public hearing in April 2012. A meeting was organised on 28 August 2012 in Amsterdam to present the first draft of the national plan for rare diseases.

A second draft was presented on the website in January 2013. The National Plan for Rare Diseases with input from all stakeholders is in an advanced stage of preparation, anticipated to be ready before September 2013. The national plan will consist of issues on information, care, research, availability of knowledge (education), availability of therapy, awareness and the role of Patient's organisations.

Centres of expertise

All stakeholders – and also the government - support the idea that the (follow-up) care and research for patients with rare diseases should be concentrated in, and/or coordinated from, a limited number of centres, in order to guarantee expert care and to stimulate research. In order to stimulate the development of centres of expertise in the Netherlands the Steering Committee on Orphan Drugs developed criteria for expertise centres together with different stakeholders (hospitals, doctors, patients, researchers). These criteria are in line with the criteria established by the EUCERD. The Dutch Government asked the University Medical Centres to work on a plan for concentration of rare disease expertise.

The Dutch Federation of University Medical Centres (NFU) presented their plan at the Conference on the National Plan in August 2012. Here it was stated that the NFU will present their 'list' with centres of expertise early 2013. This list with identified centres will be checked with the information in the Orphanet database and the information collected by the National Patient Alliance for Rare and Genetic Disease (VSOP) . If the NFU does not complete this procedure, the Ministry of Health will do so on their behalf. The government has also decided that only University Hospitals can be reimbursed for orphan drugs. Centres are designated at the moment in this way.

Registries

There is no comprehensive national patient registry in the Netherlands, or designation process, but several patient registries exist for specific rare diseases, including registries maintained by patient organisations and at the main clinical reference centres.

The expertise of several partners involved in the research of rare inborn errors of metabolism (IEM) has been assembled in the Orphan Disease Registry Consortium. Pooling of expertise will greatly support registry of these metabolic diseases in The Netherlands and will lead to improved guidelines for treatment and monitoring as well as a better understanding in the future. This project delivered one thesis in 2012: Fabry

disease; studies on diagnosis, screening and patient's perspective. Another result of this project is that the national web-based facilitating registry for inborn errors of metabolism has been further developed³³¹.

To assist patient organisations in the setting up of patient registries and biobanks, VSOP launched the website www.biobanken.net.

A registry of all patients referred with an abnormal neonatal screening result (NEORAH) has been put into place at the RIVM (National Institute for Public Health and the Environment) for two rare diseases (AGS and sickle cell disease). Furthermore the Netherlands contributes to European registries including ECARUCA, EIMD, TREAT-NMD, AIR, EURO CARE CF, EPCOT, X-ALD and EUROCARE.

Neonatal screening policy

In the current neonatal screening program in the Netherlands 18 rare disorders are diagnosed: phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis (2010), biotinidase deficiency, galactosaemia, glutaric aciduria type I, HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, maple syrup urine disease, MCAD deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, sickle cell disease, tyrosinemia type I, longchain hydroxyacyl-CoA dehydrogenase deficiency and very-long-chain acyl-CoA dehydrogenase deficiency.

The Dutch Health Council has been asked by the Ministry of Health to present their advice about expanding neonatal screening for other (rare) diseases. Screening is not primarily oriented towards rare diseases, but aimed at those diseases for which some form of treatment is available. In other words establishing a diagnosis in a patient via screening should in theory lead to a gain in health. This can also be the case for rare diseases.

Genetic testing

All eight University Medical Centres are licensed for clinical genetics; to provide counselling and pre- and postnatal testing. Services include genetic counselling, chromosome analysis, biochemical (enzyme) diagnostics and DNA-diagnostics. Genetic counselling is offered locally or in out-clinics affiliated to the centre. All services are offered regionally except for the DNA-diagnostics which, since their start in 1988, operate at a national level. Preimplantation Genetic Diagnosis (PGD) is offered in one University Medical Centre, being connected with several other genetic centres by 'transport PGD'. Patient request for PGD for new genetic indications are seen by both a local and national PGD ethics committee.

All genetic laboratories are accredited according to ISO 15189 (international standard for medical laboratories). Each DNA laboratory provides a specific package of gene tests; tests for the more frequent genetic disorders, like breast cancer are offered by more centres. Tests for rare diseases are usually performed in one laboratory only, but the rare disease diagnostics is in flux due to the application of multigene packages for heterogeneous disorders and the emergent application of the whole genome sequencing. Expertise and research is leading in the portfolio of tests offered. Diagnostic tests for 1064 genes and an estimated 1005 diseases are registered in the Orphanet database³³².

Genetics services in the Netherlands are funded by the private health insurance companies through a special budget. Diagnostic tests are reimbursed on the condition that there is a medical reason to do this test. For tests that are not available in the Netherlands, samples can be sent abroad. Molecular genetic laboratories have distributed the tests according to specific expertise that is available.

National alliances of patient organisations and patient representation

VSOP is the Dutch national alliance of patient organisations for rare and genetic disease, representing 67 of such organisations in The Netherlands (www.vsop.nl). VSOP deals with specific, mutually shared issues related to rare and genetic disease in health care policy; perinatal care, including preconception care; biomedical research; prevention; standards of care; orphan medicines, paediatric medicine, ethical and societal issues. VSOP works in partnership with other Dutch patient umbrella organisations (NPCF, CG-Raad, PlatformVG) that are dealing with issues that may also affect people with rare disorders.

VSOP has an equal voice in several national governmental bodies dealing with health care and research policy relevant to rare diseases: the Dutch Health Council (Gezondheidsraad), the national PGD committee, the RIVM prenatal and neonatal screening committees, the Forum Biotechnology and Genetics, ZonMw, CBG advanced therapy committee, etc. VSOP works in partnership with both member and non-member patient organisations to improve quality of care, quality of life and to stimulate research. With regards

³³¹ <https://ddrmd.nl/index.php/>

³³² Data extracted from orphanet in December 2012.

to the designation of centres of expertise, VSOP works together with Orphanet and the umbrella of academic medical centres (NFU) to bring in the patient perspective and stimulate quality and cooperation. VSOP actively participates in the development and future implementation of the Dutch National Plan for Rare Diseases.

Most disease specific organisations in The Netherlands, including organisations for rare diseases, receive between €25,000 and €35,000 governmental funding per year. The VSOP was successful in the acquisition of project grants from other sources, like governmental funds, charities and EU-funded programs, making it possible to have about 15 employees working for the quality of life of people with rare and genetic diseases and their families. However, the structural governmental funding of VSOP will end per 2014.

In addition the VSOP and all other patient organisations receive vouchers, worth €18,000, to be combined with 6 other vouchers (patient organisations) to realize patient-driven projects. In total 18 projects started with 201 vouchers from patient organisations. Three vouchers projects were specifically dedicated to rare diseases, with a total budget of €1.5 million

VSOP has a strong European and international orientation. It represents the European patient umbrella EURORDIS in The Netherlands and participates on behalf of EGAN (www.egan.eu) in several European projects (e.g. Gencodys, GRIP, ECRIN-IA, EUPATI, Europlan, and currently in negotiation: Asterix and Closed) and committees, like the COMP at EMA, London and the ESHG Quality Committee. VSOP also initiated 'Preparing for life' an international strategy for preconception care. In 2012, cooperation in this field started with WHO.

Sources of information on rare diseases and national help lines

Orphanet activities in the Netherlands

Since 2004, there is a dedicated Orphanet team in the Netherlands, currently hosted by the Leiden University Medical Centre. The Leiden University Medical Centre was designated by the Ministry of Health, Welfare and Sport in 2010 as the official Orphanet team for the Netherlands. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, bio banks, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Netherlands³³³ national website in Dutch which was launched in 2011.

A collaboration has been established between Orphanet and the Erfocentrum, the Dutch National Genetic Resource and Information Centre. Erfocentrum provides information about genetic diseases to the Dutch general public and for that purpose it has written Dutch abstracts for approximately 500 rare genetic diseases. All of these abstracts are validated by clinical geneticists and patient organisations. This collaboration allows Orphanet to use the Erfocentrum abstracts to provide information about rare diseases to the Dutch-speaking public. Hyperlinks, leading to the Erfocentrum website containing the Dutch abstracts, will be added to the disease-pages on Orphanet.

Starting February 2012, the entry of new specialised Dutch clinics in the Orphanet database is validated by the Scientific Advisory Board of Orphanet the Netherlands. Being represented in this board, VSOP contacts patient organisations to give their perspective on applications of (candidate) centre, using the EUCERD criteria.

Official information centre for rare diseases

As of 31 December 2011, the Steering Committee was disbanded by the government: however ZonMw (the Netherlands Organisation for Health Research and Development) was stimulated to install a general information desk at the secretariat for rare diseases with as main objective to coordinate the plan on RD (NPZZ). With a small financial incentive (€30 000) ZonMw has stimulated the development of new information portals for researchers and small pharmaceutical companies about orphan drugs. After this project this portal should be embedded within the Dutch Pharmaceutical Umbrella Organisations: Biofarmind and Nefarma.

Help line

The most used help line for rare disorders is the Erfocentrum ERFO line, providing information on genetic and rare diseases and pregnancy/reproduction related questions. This line can be reached by phone and e-mail.

The Royal Dutch Association of Pharmacists (KNMP) has developed in collaboration with the Steering Committee on Orphan Drugs the website www.farmanco.knmp.nl/weesgeneesmiddelen which publishes practical information on European registered orphan medicinal products, in particular for pharmacists but patients can also make use of it.

³³³ <http://www.orpha.net/national/NL-NL/index/homepage/?!ng=FR>

Information on neonatal screening is available from the National Institute for Public Health and the Environment (RIVM)³³⁴, both for the general public, parents and physicians. Information is also provided by the many Dutch patient organisations, pharmaceutical companies and the Federation of University Hospitals, etc.

Other sources of information on rare diseases

The most specialised and most used website for rare disorders is the National Genetic Resource and Information Centre Erfocentrum site www.erfelijkheid.nl, providing information on genetic and rare diseases and pregnancy/reproduction related questions. The Erfocentrum has a board of representatives of both patient organisations and medical professionals and hosts the national helpline for information on genetic issues and rare diseases. The website www.erfelijkheid.nl contains a database of approximately 500 rare diseases with information for both lay-persons and professionals. In 2013, 50 new rare diseases (all chromosome disorders) will be added to the database. In addition, public information is available on genetic, biomedical and pregnancy related issues³³⁵. Since 2010 videos were added to the website. In 2012 ten new videos were produced and added. Using videos, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

While www.erfelijkheid.nl is successfully reaching an audience of patient, their family and the general public, Erfocentrum also participates in the website www.huisartsengenetica.nl, which focuses on general practitioners. Erfocentrum also provides news on genomics and rare diseases via email to more than 100 patient organizations and via Twitter to over 400 medical professionals and organisations.

Good practice guidelines

VSOP hosts a website dedicated to good practice guidelines for rare diseases. On this website, www.zorgstandaarden.net, standards of care for rare diseases developed by VSOP are published, to be used by healthcare providers. Both generic themes and disease-specific standards are worked out. In addition, in 2012 VSOP finished 33 treatment guidelines for general practitioners carried out in close collaboration with the related patient organisations and the Dutch College of General Practitioners (NHG). Ten additional guidelines are in preparation.

Clinical guidelines on mitochondrial diseases and on Guillain-Barré syndrome (GBS) were launched in 2012. The alliance for Neuromuscular Diseases developed in cooperation with medical specialists specific information for GBS which patient can take with them (to the GP and others), in line with the project 'Patient as information carrier'. The patient organisation VKS (Adults, Children and Metabolic disorders) developed 20 new healthcare pathways for metabolic diseases.

Training and education initiatives

At governmental level, training and education initiatives in the field of rare diseases are not foreseen, because these are the remit of universities and professional organisations. The Boerhaave Committee (at Leiden University Medical Centre) organises the annual Princess Beatrix Fund Symposium on Neuromuscular Diseases for medical specialists and their assistants. There is still a growing interest at college and university students to write a paper on rare diseases or orphan medicinal products.

Training for health care providers on prenatal and neonatal screening is organised at a regular basis by the National Institute for Public Health and the Environment. Documents used in training are available at the website³³⁶.

National rare disease events in 2012

Several parties (ZonMw, Rare Disease Fund ZZF, KPMG and VSOP) worked together to organise the fifth National Rare Disease Day, on 25 February at the Dolfinarium in Harderwijk, as part of the international rare disease day coordinated by Eurordis. Angel Awards were granted to a patient representative and a medical specialist as a recognition, reward and encouragement. Over 500 people attended this day, which generated a lot of media attention.

Hosted rare disease events in 2012

In 2012 the following rare disease related events were hosted by the Netherlands and reported in *OrphaNews Europe*: Eurogentest2 General Assembly (Nijmegen, 18 January 2012), Joint Eurogentest/Techgene Scientific

³³⁴ www.rivm.nl/pns/hieiprik

³³⁵ These sites provide further web based information: www.biomedisch.nl; www.zwangernu.nl; www.zwangerwijzer.nl; www.slikeerstoffoliumzuur.nl; www.prenatalescreening.nl

³³⁶ For instance information for screeners and information on the diseases screened: www.rivm.nl/pns/hieiprik/films.

Symposium (Nijmegen, 19 January 2012), Symposium on Neurocognitive Developmental Disorders (Rotterdam, 25 May 2012), 11th Conference of the International Association of Bioethics: Bioethics and the Future, and the Future of Bioethics (Rotterdam, 26-29 June 2012), The Second Joint International Symposium on Neuroacanthocytosis and Neurodegeneration with Brain Iron Accumulation (Ede, 26–27 October 2012), 12th International symposium on MPS and related diseases (Noordwijkerhout, 28 June - 1 July 2012).

Research activities and E-Rare partnership

National research activities

A multi-annual research programme started in 2011 at The Netherlands Organisation for Health Research and Development (ZonMw) with a funding of €13.4 million. The main objective of this is to stimulate translational research in rare diseases with the aim of developing therapies. Three projects were each awarded a €3 million grant under this ZonMw Priority Medicines for Rare Diseases and Orphan Drugs (PM Rare) research programme³³⁷. The projects involve research that could potentially lead to new therapies for rare diseases and are to be carried out by public-private partnerships. Those selected are: antisense therapy for several major rare diseases; gene-corrected stem cells for curative treatment of severe combined immunodeficiency; and towards treatment of MELAS syndrome: drug development based on newly identified compounds.

ZonMw, the Netherlands Organisation for Health Research and Development, funds health research and stimulates use of the knowledge developed to help improve health and healthcare in the Netherlands. ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research. Within several ZonMw programmes, RD research is financed (e.g. Efficacy research OD, Stem cell and Gene therapy, HTA, screening)³³⁸

There are tax reductions for R&D in high-tech start-ups from which orphan medicinal product companies can benefit. There are also several programmes from the Ministry of Economic Affairs to facilitate start-ups and SME's (Innovation Fund) that orphan medicinal product companies can benefit from.

In 2011, the Netherlands Organisation for Scientific Research made €22.5 million available to a consortium including 8 Dutch University Medical Centres and other research institutes and universities in order to establish a national biobanking infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure Netherlands (BBMRI-NL), which will integrate clinical materials and data gathered over many years with the goal of improving access to human samples. Such samples are important to rare disease and orphan medicinal product research. In 2011, 26 new projects started. In the databank are (October 2012) 191 Dutch Biobanks and over 500 000 participants. In 2013 new projects will be able to be granted.

The VU University Medical Centre in Amsterdam is working together with the Dutch Neuromuscular Diseases Association in the development of an n-of-1 trial service. The project investigated whether such trial treatments, to be facilitated by the n-of-1 trial service, could be reimbursed by the Dutch basic health insurance. It is also examining whether the results of this type of research may be sufficient for authorities to decide on the effectiveness of an off-label medicine and its reimbursement for future patients with the rare disease in question.

Participation in European research projects

The Netherlands participates, or has participated, in European rare disease research projects including: AIPGENE, ANTEPRION, ANTIMAL, BIGHEART, BIONMD, BALANCE, CELL PID, CARDIOGENET, CURE-FXTAS, CHEARTED, BIOMALPAR, BNE, CELL-PID, CONTICANET, CURE-FXS, CRUMBS IN SIGHT, ELA2-CN, DRUGSFORD, DIALOK, DSDLIFE, EDAR, EMVDA, EMINA, EMINA2, Eur-USH, EURODBA, EUCLYD, EuPAPNet, ESPOIR, EUROSARC, EUROMOTOR, EURO-CGD, EUMITOCOMBAT, EUNEFRON, EUROBONET, EURAMY, EUROCARE-CF, EUROGENTEST 1&2, EUROGLYCANET, EUROMEDICAT, ENS@T, EURENOMICS, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, EVI-GENORET, EUROSD, EUROPADNET, EUROSTEC, HSCR, GAPVAC, GRIP, GENESKIN, GEN2PHEN, GENTECH, GENCODYS, GRIP, HDLOMICS, INTREALL, ENCCA, IMMUNOPRION, MLC-TEAM, NEMMYOP, NSEuroNet, NEUROMICS, NEUROSIS, NMD-CHIP, NOVSEC-TB, MITOCIRCLE, MITOTARGET, MMR-RELATED CANCER, MYASTAID, NEUROPRION, OLIGOCOLOR, OVER MyR, PPPT-MJD, PYRAMID, PEROXISOMES, PERSIST, PNSEURONET, PRIBOMAL, PWS, TB-DRUG, TARGET-CdLS, TREAT-NMD, VACCINES4TB, VITAL, Splice-EB, RDCONNECT, RD PLATFORM, and REVERTANT-EB.

³³⁷ <http://www.zonmw.nl/nl/programmas/programma-detail/priority-medicines-zeldzame-ziekten-en-weesgeneesmiddelen-rare/algemeen/>

³³⁸ <http://www.zonmw.nl/nl/themas/thema-detail/zeldzame-ziekten-en-weesgeneesmiddelen/thema-detail/>

E-Rare

The Dutch Organisation for Health Research and Development (ZonMw) participates in E-Rare 1 (2006-2010) and E-Rare 2 (2010-2014), and participated in the 4th Joint Transnational Call in 2012: teams from the Netherlands participate in 8 out of the 11 consortia selected for funding

IRDIRC

The Netherlands Organisation for Health Research and Development (ZonMw) and the pharmaceutical enterprise Prosensa are committed members of the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee³³⁹

In 2011 the Steering Committee focused on the draft for a national plan in close cooperation with different stakeholders. However, it was decided that the Steering Committee would not be funded by the Dutch government after December 2011 and no longer existed as a governmental committee from 2012 onwards. Stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise in the future with the Netherlands Organisation for Health Research and Development ZonMw taking more responsibility and assuming a number of tasks from the former Steering Committee. Notably, the coordination of the development and implementation of a national strategy will be from 2012 onwards assumed by a secretariat at ZonMw and the sounding board on the National Plan. This plan will not only cover Orphan Drugs but also Rare Diseases.

Orphan medicinal product incentives

A waiver can be granted for the registration fee of a medicinal product if the medicinal product is already registered in one or several other EU member states and if the prevalence of the indicated disease is less than 1 in 200.000 inhabitants in the Netherlands. In the case of orphan medicinal products for a rare disease for which no alternative treatments exist, there is no obligation for companies to provide pharmacoeconomic data. In individual cases this may also be the case for orphan medicinal products for a disease with a prevalence no more than 5 persons per 10,000 for which an alternative treatment does exist.

The programme for Expensive and Orphan Medicines (2007-2014) aims to investigate the effectiveness of expensive drugs and of expensive orphan medicinal products and the development of HTA methodology to help the Dutch Health Care Insurance Board in its advice on reimbursement. In the scope of this programme, several projects on registered orphan medicinal products have already been selected. As of 1 January 2009, the subsidy scheme Orphan Designation Dossier (ODD) is in action. This is an initiative of the Dutch Steering Committee on Orphan Drugs and is executed by the Netherlands Organisation for Health Research and Development (ZonMw). This initiative will help stimulate the development of orphan medicinal products in the Netherlands by providing Dutch pharmaceutical Small and Medium-sized Enterprises (SMEs) a small subsidy for the costs of writing and submitting the ODD to the EMA.

Orphan medicinal product market availability situation

In the Netherlands, all orphan medicinal products with EU market authorisation are available on the market. The government decides which of the products will be reimbursed. Therefore it is necessary to file a reimbursement dossier at the Dutch Health Care Insurance Board (CVZ), the advisory body concerning reimbursement. If there is no registered drug for a rare disease, the treatment can be paid for if the disease is very rare (less than 1 in 150 000 inhabitants) and there no other alternative and there is scientific evidence about using the drug for the specific disease. Costs are covered by the health insurer, the health care insurance company can obtain scientific advice at CVZ about evidence.

Orphan medicinal product pricing policy

The minister will start the negotiation with pharmaceutical companies about pricing (*see evaluation of conditional reimbursement in the section below*).

Orphan medicinal product reimbursement policy

In the Netherlands the following orphan medicinal products are reimbursed: Aldurazyme, Arzerra, Carbaglu, Cayston, Cystadane, Diacomit, Elaprased, Evoltra, Exjade, Fabrazyme, Firdapse, Glivec, Increlex, Kuvan, Lysodren, Mepact, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Prialta, Replagal, Revatio, Revlimid,

³³⁹ Also the former Dutch Steering Committee OD had a broader assignment than only OD.

Revolade, Signifor, Siklos, Soliris, Somavert, Sprycel, Tasigna, TOBI podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, Wilzin, Xagrid, Yondelis, Zavesca.

The following orphan medicinal products are available when ordered by a physician or a pharmacist either through a hospital budget or on a named-patient basis: Atriance, Busilvex, Ceplene, Esbriet, Firazyr, Gliolan, Inovelon, Litak, , Mozobil, Pedeia, Photobarr, Peyona, Plenadren, Riloncept Regeneron, Savene, Tepadina, Thalidomide, Trisenox, , VPRIV and Vyndaquel.

In 2012, the Dutch Health Care Insurance Board (CvZ) addressed the country's Minister of Health concerning the conditional reimbursement of three rare disease products deemed "too expensive". These products target lysosomal storage disorders: a treatment for Pompe disease and Fabry disease treatment. Health Minister Edith Schippers has been advised to cut public funding for the treatments, although babies diagnosed with Pompe disease would continue to have their treatment supported by State funding under the proposal. The minister will start the negotiation with pharmaceutical companies about pricing. During this negotiation the drugs will be reimbursed (in 2013).

Other initiatives to improve access to orphan medicinal products

A physician may prescribe non-authorised drugs (e.g. drugs, including orphan medicinal products, authorized elsewhere or even not authorised anywhere), but only with an approval of the Health Inspectorate. The prescribed drug is not reimbursed, unless the health insurer chooses to do so. Apart from these provisions, there are no other initiatives regarding access.

Other therapies for rare diseases

No specific information reported.

Orphan devices

There are no (new) initiatives regarding orphan devices.

Specialised social services

Respite care services are available, imbedded in the general health care system.

1.20. POLAND

Definition of a rare disease

In Poland, there is no official definition for rare diseases; however the definition from the regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products of a prevalence of no more than 5 in 10 000 individuals is widely used amongst stakeholders. In Poland this equates to less than 1 900 000 patients (around 5% of the population).

National plan/strategy for rare diseases and related actions

By the end of 2012 a strategic document "National Plan for Rare Disease – the roadmap" was prepared and handed to the Minister of Health. A broad consultation process started, and it is scheduled for completion by June 2013 in order to meet the recommendations of the EU Council by the end of 2013.

The existing National Health Program 2007-2015³⁴⁰ (health policy paper elaborated by the office of the Prime Minister) covers some issues of the rare diseases in broad understanding of public health. Among the 8 strategic goals addressing main causes of mortality in Poland there is the mention of rare diseases, but they are not exclusively designated. There is currently no specific budget dedicated for rare diseases within the framework of the entire health care system, however specific health interventions are reimbursed in project mode (e.g. therapeutic programs). This does not mean that the treatment of rare diseases is ignored. All diagnosed rare disease cases are treated in the framework of health care system. When reimbursement of orphan medicinal products is possible (within the basket of reimbursed services), therapeutic programs are in place, with an annual budget (2012) equivalent to €33,5 million (same as 2011).

³⁴⁰ http://www.mz.gov.pl/wwwfiles/ma_struktura/docs/zal_urm_npz_90_15052007p.pdf (web site valid march 2013)

The Rare Disease Task Force, the advisory body to the Minister of Health, initially appointed in 2008, was reorganised in late 2011 to meet new expectations of preparing strategic paper "National Plan for Rare Diseases – the roadmap". Chaired by representative of the Ministry of Health it consists of: four experts in the field of rare diseases including representative of umbrella patient organization, representatives of Poland in the EU institutions in the field of rare diseases, Directors of the Departments at the Ministry of Health and representatives of National Health Fund (the payer).

Upon the occasion of International Rare Disease Day celebration in Warsaw (29 February 2012), the National Forum for the Therapy of Rare Diseases handed the proposals for the National Rare Diseases Plan to the Minister of Health, expecting its further elaboration and adoption. The Minister of Health declared, that by the end of 2012 the draft paper "National Plan for Rare Disease – the roadmap" will be completed by Rare Disease Task Force. On the same day the Parliamentary Group on Rare Diseases met to contribute to the drafting process.

In Spring of 2012 another initiative of the self-organised "Partnership for the National Plan for Rare Diseases" (RD think-tank, consisting of representatives of patients groups, academia, clinicians, health politics, payer, providers, suppliers and communication) started its work. Actively supported by the Chairman of the ministerial Rare Diseases Task Force as well as the Children's Memorial Health Institute, the series of working meetings took place in order to broadly discuss the final draft of each area of the National Plan. During six workshops and number of satellite meetings, the final text was elaborated.

Between February and December 2012, the Rare Disease Task Force met eight times to elaborate and draft 12 consecutive versions of the paper. Parallel work in Parliamentary Group on Rare Diseases as well as Partnership for the National Plan for Rare Diseases group was a significant support.

The entire initiative was launched following the recommendation of the EU Council on the involvement of patients and their representatives in the political process and promoting the activities undertaken by rare diseases patient groups and associations.

In summary, during entire 2012, a total of 42 meetings, consultations, workshops and conferences were held, with active participation of group of ca 400 experts (clinicians, scientists, patients groups, providers, payers, industry, Members of Parliament, Government Officials, health politicians) to work on the document entitled "The National Plan for Rare Diseases – the roadmap". The final version (no 12.2) was submitted to the Ministry of Health in December 2012, as scheduled. Accordingly to the project plan, the final paper should be signed by the Minister of Health before June 2013. Later on work on organisational, budgetary and legal framework will take place, based on the strategic paper "The National Plan for Rare Diseases – the roadmap" which has been accepted by the Ministry of Health and the Government.

Centres of expertise

In Poland, the healthcare provision for patients with rare diseases is not organised in a specific framework and there are no official centres of expertise for rare diseases. Around 10-15 centres have a reputation for expertise in a given field and conducts diagnostics and treatment to different extents. For instance there is a national coordinating centre for metabolic rare diseases at the Children's Memorial Health Institute in Warsaw with links to regional centres. There is the intention to establish a designation policy for centres of expertise.

Registries

There is no national committee dealing with registries, however the Centre of Information Systems has the responsibility to facilitate the Parliament Act of April 2011 on information systems in healthcare, which is in force since January 2012. It states that all registries have to comply with strict requirements, including data safety and protection. Registries had to comply with its requirements by June 2012 including measures for data safety and protection. The Minister of Health in the field of monitoring of healthcare needs, patients health status, prophylaxis and monitoring of health programs, may establish a dedicated registry, issuing a particular Regulation, which may also state a public source of funding. Although this legal regulation is in force, there is no designation process for a unified rare disease registry at the moment.

So far a number of registries by Academia and clinicians are in place, such as the National Registry of Paediatric Cancers and the Polish Registry of Congenital malformations.

Poland takes part in the European registries such as EIMD, EHDN, ESID, ERCUSYN, TREAT-NMD, EUROCARE CF, EUROWILSON, EUROGLYCAN, EURO-WABB, SCNIR, RARECARE, and EUROCAT.

Neonatal screening policy

There is a national newborn screening program for phenylketonuria, congenital hypothyroidism, cystic fibrosis and congenital deafness, under Ministry of Health Regulation. Metabolic newborn screening is coordinated by

the Institute for Mother and Child in Warsaw, while congenital deafness (collaboration with NGO – The Great Orchestra for Christmas Charity) by Poznań Medical University.

An additional 20 metabolic disorders can be diagnosed using tandem mass spectrometry (MS/MS): this is available in some regions (8 of 16 voivods in Poland, which covers around 60% of the Polish population) through a Ministry of Health financed programme (till 2014).

Genetic testing

There are about 35 laboratories (public and private) offering testing for rare diseases. There are no officially designated reference laboratories. Most of them follow external quality control assessments. Diagnostic procedures which are performed in these labs mainly focus on: specific genetic diseases (chromosomal and monogenic disorders), metabolic diseases (selective screening testing for inborn errors of metabolism, lysosomal storage disorders, neuromuscular and haematological diseases, defects in metabolism of carbohydrates, fats, amino acids, purines and pyrimidines, neurotransmitters, as well as disturbances of calcium-phosphate metabolism and energetic processes).

If it is not possible to diagnose a specific disease in Poland the National Health Fund (the payer) may reimburse diagnostic procedures on demand, after a referral (second opinion scheme) from the Regional Consultant in genetics.

Diagnostic tests are registered as available in Poland for 199 genes and an estimated 289 diseases in the Orphanet database³⁴¹.

National alliances of patient organisations and patient representation

The National Forum for the Therapy of Rare Diseases – ORPHAN, founded in 2005, serves as national alliance for rare disease patients' organisations in Poland. As the umbrella for rare disease associations, the Forum groups together 24 rare diseases patient organisations and it strengthens the cooperation at the national level. The representative of the National Forum was appointed by the Minister of Health as the member of the Rare Disease Task Force, representing the single unanimous voice and position of Polish rare diseases patient organisations during the process of drafting the "National Plan for Rare Diseases – the roadmap". More information about the goals, membership and activities of the organisation are published online³⁴².

Sources of information on rare diseases and national help lines

Orphanet activities in Poland

Since 2006 there is a dedicated Orphanet team in Poland, currently hosted by the Children's Memorial Health Institute, in 2010 designated by the Ministry of Health as a partner for the Orphanet Europe Joint Action. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Poland for entry into the Orphanet database.

Since April 2011 the Orphanet Poland team maintains a national Orphanet Poland national website³⁴³. In order to improve access to information on rare diseases, orphan medicinal products and Orphanet in Poland, the Polish Orphanet team has translated the documents concerning Orphanet's activities (leaflets), created lists of Polish associations/expert clinics/diagnostics centres and is developing Polish versions of rare disease abstracts and Orphanet Activity Report 2012. Information is available on the Orphanet website.

Orphanet Poland took part in elaborating "The National Plan for Rare Diseases – the roadmap" by participating in Ministry of Health Rare Disease Task Force, and a series meetings with patient organisations and workshops dedicated to rare diseases which took place in September 2012 in the Children's Memorial Health Institute. Polish Orphanet Coordinators were group leaders of two workshops "Support activities for the preparation of applications for research projects related to rare diseases" and "Exchange of information to gather knowledge about centers of expertise in Poland; Creation of centers of expertise for group of rare diseases based on currently operating centers treating patients with rare diseases; Support for the creation of reliable registries for rare diseases".

Official information centre for rare diseases

There is no official information centre on rare diseases in Poland other than Orphanet.

³ Information extracted from the Orphanet database (December 2012).

³⁴² www.rzadkiechoroby.pl/np

³⁴³ www.orpha.net/national/PL-PL

Helpline

There is currently no national help line for rare diseases. Some patient organisations run help lines for specific rare diseases.

Other sources of information

No specific activity currently reported.

Good practice guidelines

No specific activity currently reported.

Training and education initiatives

There are some rare disease specific training sessions for professionals. The best known are dysmorphology meetings organised by the Children's Memorial Health Institute (CMHI) in Warsaw, which have been organised on a regular basis for 4 years now, initially as a part of the Dyscerne project. The Department of Medical Genetics of CMHI have organised the course for paediatricians concerning on advances of molecular biology in paediatrics. In addition, some metabolic rare diseases are also presented and discussed during sessions organised every year by the Medical Centre for Postgraduate Education in Warsaw dedicated to the training of physicians or professionals being trained specific medical speciality (paediatricians, neurologists and child neurologists, clinical geneticists etc.).

National rare disease events in 2012

Rare Disease Day was marked in Warsaw on 29 February 2012 with a conference entitled "Strong Together". Around 120 people participated (including Minister of Health) and the media were present. There was a special portal opened for the occasion: www.dzienchorobrzadkich.pl. There was also a photo exhibition depicting people with rare diseases. A social media campaign entitled "Hope. It's in your genes" was launched that day for at least 1 year run. It still operates as the biggest national rare diseases awareness campaign at www.nadziejawgenach.pl. During the Day, there was also the opportunity to educate students about rare diseases by lectures and information points around Poland in many medical high schools and universities. These activities continued nationwide during 2012.

Other events included: Selected Aspects of the Genetics of Metabolic Diseases (9-13 January 2012, Warsaw), unknown dysmorphological cases (20 April 2012, Warsaw), Polish Smith-Lemli-Opitz syndrome Society Conference (30 April - 3 May 2012, Warsaw), Pediatric cardiology course (7-11 May 2012, Warsaw), 10th European Conference on Rare Diseases (6-9 July 2012, Cedzyna). Dysmorphologic meeting during Conference "Options to support the development of people with Duchenne's disease and other muscular dystrophies" (30 November, 2012, Sobieszewo/Gdańsk).

Hosted rare disease events in 2012

Amongst the hosted events organised in 2012 was the 9th European inborn errors of metabolism course in Warsaw, Poland (in collaboration with the Children's Memorial Health Institute) (Warsaw, 25-29 September 2012), and the Fourth International Meeting on Primary Central Hypoventilation Syndromes (Warsaw, 13-14 April 2012).

Research activities and E-Rare partnership

National research activities

There is no research programme specifically aimed at rare diseases in Poland. Research on rare diseases are financed within different programmes for state-funded research but there are no specifically allocated funds. Around 10% of projects approved for funding being related to the field of rare diseases. The Polish Ministry of Science and Higher Education usually allocated funding for around ten research projects dedicated to rare diseases in calls for proposals.

Participation in European research projects

Polish teams also participate/participated in European rare disease research projects including: EUROGLYCANET, ERNDIM, EUROMEDICAT, EUROCARE-CF, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROSCA, EURADRENAL, EURO-GENE-SCAN, MYELINET, IMMOMECC, NEURO.GSK3, NEUPROCF, RD PLATFORM, TB PAN-NET, SIOPEN-R-NET, ENCCA, EIMD, GRIP, TIRCON, INTREALL, EUROSARC, DSD, PADDINGTON.

E-Rare

Poland is an observer of the E-Rare 2 project. The Polish partner for E-Rare ERA-NET is The National Center for Research and Development. Poland joined the 2012 Joint Transnational Call but did not receive funding.

IRDIRC

Polish funding agencies have not committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

There is no specifically dedicated orphan medicinal product committee in Poland.

Accordingly to the new Reimbursement Act (in force since July 2011), the Economics Committee within the Ministry of Health takes responsibility to negotiate market conditions for products applying for reimbursement, including orphan medicinal products.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

In 2012 following orphan medicinal products has been reimbursed: Cerezyme, Naglazyme, Elapraze, Laronidase, Myozyme, and Cystadane.

Orphan medicinal product pricing policy

Since July 2011 Economics Committee (appointed by the Minister of Health) takes responsibility in pricing on negotiation basis with the market authorisation holder. Following their recommendation the Minister of Health issues public price and reimbursement conditions for the drug. Each medicinal product has to follow HTA requirements of the by Polish Medicinal Health Technology Assessment Agency. In addition to this, the role of HTA has been strengthened.

Orphan medicinal product reimbursement policy

The system of drug reimbursement changed on 1 January 2012 accordingly to the Reimbursement of drugs, food for special dietary use and medical devices Act, issued 12 May 2011. The new system is unified and application based. The Minister of Health is not able to introduce reimbursement of a new drug without prior official request from the Marketing Authorisation Holder. The application process is costly and has to be supported with comprehensive data (including reimbursement status, price data in other EU Member States, and health technology analysis).

Currently, drugs for some rare diseases are reimbursed through therapeutic programmes. The Minister of Health every second month (I, III, V, VII, IX, XI) announces the official order containing the list of reimbursed medicinal products. Diseases currently covered include: Crohn disease, Prader-Willi syndrome, cystic fibrosis. Additionally, six drugs for rare diseases are reimbursed for patients with Gaucher, MPS I, II and VI, Pompe disease, and hyperhomocysteinemia. Nothing has changed since September 2009, when the Minister of Health decided to limit available therapy to infantile-onset Pompe disease. Authorities question the rationale of reimbursement of therapy of late-onset Pompe disease due to "lack of proven clinical efficacy", which causes patients unqualified for reimbursed therapy.

Other initiatives to improve access to orphan medicinal products

There is no official compassionate use policy. Life-saving treatment with drugs registered outside of Poland is subject to individual decisions of the Minister of Health and might be reimbursed by the President of the National Health Fund under his consent on a named-patient basis. If a company donates a drug, it is subject to taxation, which further limits potential compassionate use. Furthermore, according to the Reimbursement Act, after the recommendation of the national authority in the field of medicine and opinion of the HTA Agency, the Minister of Health can make a reimbursement decision.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

Since 1 January 2012, according to the Reimbursement Act, the national healthcare package has been continuously supplemented by new medical devices dedicated also to patients with rare diseases. Orphan devices are regularly presented during dysmorphological meetings, national conferences and trainings.

Specialised social services

There are no social services specifically designed for patients for rare diseases, though respite care exists in general and educational centres can provide day care for children and education for patients: these are both privately and publically funded initiatives, provided on an application basis. Some official programmes require for patients to be qualified as disabled in order to participate. Therapeutic recreational services such as camps are eligible for co-funding by the state social care (usually 30% patient co-payment). Patient organisations sometimes provide services which are financed from private funds specifically for rare diseases patients. The state funds the integration of children with special needs, via "integration classes" in schools.

1.21. PORTUGAL

Definition of a rare disease

Portugal accepts the definition of rare disease, as stated in the European Regulation on Orphan Medicinal Products, as a disease with a prevalence of no more than 5 in 10 000 inhabitants. This definition has been adopted by the National Plan for Rare Diseases.

National plan/strategy for rare diseases and related actions

In November 2008 the Portuguese Minister of Health approved the National Plan for Rare Diseases (*"Programa Nacional para as Doenças Raras"*) coordinated, since November 2011, by the Department for Quality in Health at the Directorate-General of Health (DGS).

Its main objectives are the establishment and improvement of national measures, in order to satisfy the needs of people with rare diseases and their families *vis-à-vis* medical services and care, as well as the improvement of the quality and equity of healthcare provided to those people.

Such objectives will be achieved by establishing reference centres for rare diseases, by improving the access of patients to adequate care, by strengthening knowledge and awareness on rare diseases, by promoting innovation in the treatment of rare diseases and in the accessibility to orphan medicinal products, and finally, by ensuring cooperation at national and international levels, including EU countries and those countries having Portuguese as their official language.

This Plan will cover all rare diseases, though it should articulate with other priority national plans, namely with the National Plan for Oncologic Diseases (*"Programa Nacional para as Doenças Oncológicas"*).

Besides, the National Institute of Health (INSA), through its Department of Human Genetics, coordinates the National Plan for the Control of Haemoglobinopathies.

An important step in terms of implementing the National Plan for Rare Diseases took place in 2012: a specific card for the identification of people with rare diseases (*"Cartão para a Pessoa com Doença Rara"*) was developed along this year, aiming at disclosing clinical information to medical doctors and also in emergency situations. This card, to be issued by DGS is currently being tested and will be progressively distributed during 2013.

DGS, together with the ex-Office of the High Commissioner for Health, have co-funded from 2008 to 2011, for a total amount of €1.9 million, a few projects on rare diseases, which are still nowadays being developed by several patient organisations.

Centres of expertise

Presently, there are no officially designated centres of expertise for rare diseases in Portugal. However, the identification of the so-called 'Reference Centres', considered as a major priority, is expected to be initiated in 2013.

Registries

According to the latest Orphanet report (*'Disease Registries in Europe – January 2013'*) a total of 12 registries are now available in Portugal: 10 from public entities and 2 from private institutions.

Upon their own initiative, many patients are also included in international registries. A few Portuguese institutions also participate, or have participated, in European registries, such as, E-IMD, TREAT-NMD, EUROCARE CF, EUROCAT, EBAR, SCNIR, CHS, SPATAX, and EUROWILSON.

The following commissions and/or registries operate under supervision of INSA: National Commission for the Portuguese Registry of Paramyloidosis, National Commission for Lysosomal Storage Diseases, National Registry of Congenital Anomalies (*RENAC*) and National Newborn Screening Commission.

RENAC data are available since 1996. The most recent report covers the 2008-2010 period. Another report, updating existing information, is being prepared. Two informative newsletters were sent to the hospital services that collaborate with *RENAC*; to the remaining services, letters were sent renewing the invitation for their participation in *RENAC*. The information collected on *RENAC* was also integrated in the report of EUROPERISTAT system. Moreover, *RENAC* participated in the European Surveillance of Congenital Anomalies (EUROCAT) by sending data related to the Southern region of Portugal; it further participated in the annual meeting of that European Register.

Neonatal screening policy

The National Programme for Early Diagnosis ("*Programa Nacional de Diagnóstico Precoce*") started in 1979 at the former Institute of Medical Genetics and, initially, it only included the screening of phenylketonuria. *INSA* is nowadays responsible, at both organizational and laboratorial levels, for the national newborn screening programme, which covers ca. 100 % of all children born in Portugal.

Currently, the following 26 diseases are screened: Congenital Hypothyroidism, Phenylketonuria (PKU)/ Hiperphenylalaninemia, Tyrosinemia Type I, Tyrosinemia Type II/ III, Maple Syrup Urine Disease (MSUD), Citrullinemia Type I, Argininosuccinic Aciduria, Argininemia, Classic Homocystinuria, Methionine Adenosyltransferase Deficiency (MAT deficiency), Propionic Aciduria (PA), Methylmalonic Aciduria type mut- (MMA, Mut-), Isovaleric Aciduria (IVA), 3-methylcrotonyl-CoA Carboxylase Deficiency (3-MCCD), Glutaric Aciduria Type I (GA I), Methylmalonic Aciduria type Cbl C/D (MMA, Cbl C/D), 3-hydroxy-3-methylglutaric Aciduria (3-HMG), Malonic Aciduria, Medium Chain AcylCoA Dehydrogenase Deficiency (MCAD), Very Long Chain AcylCoA Dehydrogenase Deficiency (VLCAD), Long Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)/ Trifunctional Protein Deficiency (TFP), Short Chain AcylCoA Dehydrogenase Deficiency (SCHAD), Primary Carnitine Deficiency (CUD), Carnitine Palmitoyl Transferase I Deficiency (CPT I), Carnitine Palmitoyl Transferase II Deficiency (CPT II/ CACT), Glutaric Aciduria Type II (MADD).

Genetic testing

Genetic testing is available for many rare disorders, though, as in other countries, there is a significant flow of genetic testing over the borders. Diagnostic tests are registered as available in Portugal for 393 genes and an estimated 463 diseases, in the Orphanet database³⁴⁴.

Genetic tests are carried out in genetic laboratories within the National Health System (NHS), as it is the case of *INSA*³⁴⁵ (considered as the national reference laboratory), as well as in laboratories located or associated with genetic services in public hospitals, and also in private laboratories; besides, a certain number of labs offer genetic testing at universities and research institutions.

Whenever a specific test is not available in Portugal, there is a formal procedure to perform it abroad.

In 2012, the number of clinical cases sent abroad for referral amounted to 354, especially for molecular study and laboratorial genetic testing.

Genetic testing in Portugal is regulated mainly by Law no 12/2005, of 26 January 2005. This law defines, among others, the concept of health information and genetic information, the circulation of information and the intervention on human genome within the health system, as well as it establishes the procedure to collect and preserve biological products, for purposes of genetic testing or of research.

As a member of OECD, Portugal is subject to the OECD Best Practice Guidelines for Molecular Genetic Testing; Portugal also signed and ratified the Oviedo Convention.

National alliances of patient organisations and patient representation

Portugal has two alliances on rare diseases: *FEDRA* – Portuguese Federation of Rare Diseases ("*Federação Portuguesa de Doenças Raras*")³⁴⁶ and *APADR* – Portuguese Alliance of Rare Diseases Associations ("*Aliança Portuguesa de Associações de Doenças Raras*").

³⁴⁴ Information extracted from the Orphanet database (December 2012).

³⁴⁵ <http://www.insa.pt/sites/INSA/Portugues/AreasCientificas/Genetica/Paginas/LaboratorioDeReferencia.aspx>

³⁴⁶ <http://www.fedra.pt>

APADR was officially established in 2009, and since then, has developed several actions and activities with the aim of improving Portuguese health policy in the field of rare diseases, and also raising awareness to this problem.

During 2012, APADR held a conference entitled "*Rare but Strong Together*", in collaboration with ORPHANET-Portugal, which took place on Rare Disease Day. Also for this particular day, APADR made a special spot, broadcasted by the radio and TV channels. APADR attended the European Conference on Rare Diseases and Orphan Products - 2012 held in Brussels, as well as the General Assembly of Eurordis.

APPDH (the Haemoglobinopathies Association and a member of APADR) organized a health fair in April and from May to December a national *roadshow* named '*In-loco Haemoglobinopathies*'. This Association also published a brochure '*Globi's Friends*', with life stories of patients and their relatives.

In 2012, RARÍSSIMAS (the largest Association within FEDRA) launched a series of events and meetings in order to raise awareness on rare diseases and to achieve several goals. Among these initiatives, they published in February "*Vidas Raras*" (Rare Lives), a book telling stories about patients and their families. Moreover, they also signed a protocol aiming to find a place to install the "*RarÍSSIMO Centre*" in Pico Island, Azores. In November they also organized in Oporto the first Meeting on '*Angelman Syndrome*' with Portuguese and international specialists. RARÍSSIMAS continues to publish its magazine '*Rare Pages*', disclosing important information on rare diseases to the whole population.

Sources of information on rare diseases and national help lines

Orphanet activity in Portugal

The national team of Orphanet has kept available and updated in Portuguese all menus from the international site³⁴⁷, all the diseases names, the emergency guides and summaries of diseases (validated by experts in each area).

This is an important resource also for all countries of official Portuguese language and the Portuguese communities spread throughout the world (about 240 million Portuguese speaking persons). The team also maintained and kept updated the Orphanet-Portugal website page³⁴⁸, and a Facebook page³⁴⁹, which have included updated news about initiatives on rare diseases in the country and in Brazil.

By the end of 2012, nearly 400 abstracts of rare disease and 18 emergency guidelines had been translated and validated into Portuguese and entered in the international database; about 150 new abstracts were also translated and validated, waiting to be inserted.

During 2012, Orphanet-Portugal continued to collect and validate and significantly increased the information available in the country on national resources and activities related to rare diseases and orphan drugs. These included 133 specialised centres, 114 diagnostic laboratories, 705 diagnostic tests, 157 research projects, 21 clinical trials, 73 patient organisations and 21 patient registries and databases, by December 2012; the list of the orphan drugs available in the country (currently 51, in a total of 88 different presentations and/or dosages) is regularly updated by INFARMED and provided in our national website, together with the annual uptake for each one.

The Orphanet-Portugal team also contributed to the development (in English) and subsequent translation and validation into Portuguese of a leaflet on "Genetic Testing Related Health", produced by the Council of Europe and prepared by EuroGentest (a network of excellence funded by the European Commission) and the PPPC (Public and Professional Policy Committee) of the ESHG (European Society of Human Genetics). This brochure (in Portuguese) is to be released during the Rare Disease Day 2013.

The national scientific advisory board of Orphanet-Portugal proved to be a valuable resource, providing important information as well as the validation of some data whenever requested; it met once, before the DNA Day event with Ségolène Aymé, leader of the Joint Action Orphanet Europe.

In addition, as in previous years, the national team has been committed to the diffusion of the Orphanet portal and services to professionals involved in rare diseases, as well as to patients, families and the general public. This was done both through the organization of specific events, and the participation in several scientific meetings and courses with oral or poster communications and lectures. In 2012, 11 presentations about Orphanet were made at such meetings, and 2 conferences were organised (together with APADR) by Orphanet-Portugal (the Rare Disease Day 2012 and a special DNA Day Conference).

³⁴⁷ <http://www.orpha.net/consor/cgi-bin/index.php?lng=PT>

³⁴⁸ <http://www.orpha.net/national/PT-PT>

³⁴⁹ <https://www.facebook.com/Orphanet.PT>

All this information is intended to help improving and shortening the time before a diagnosis is obtained, and specialised care and treatment of patients with rare diseases is reached, as well as planning and improving the care for persons with rare diseases in the country.

Official information centre for rare diseases

Orphanet is mentioned in the National Plan for Rare Diseases as the main source of information regarding activities related to rare diseases in Portugal.

Help line

The patient organisation *RARÍSSIMAS*, with funding from *DGS*, implemented in 2009 a dedicated call centre, the so-called 'Rare Line' ("*Linha Rara*")³⁵⁰, that throughout the year of 2012 provided relevant information to 2 137 requests.

Several other patient associations, as the Portuguese Haemophilia Association, also give advice and support to patients and their families, either online, by email or by phone.

Other sources of information on rare diseases

The Orphanet-Portugal team also deals with many requests for information coming from Portuguese speaking countries.

Good practice guidelines

DGS, in collaboration with the Portuguese Medical Association ("*Ordem dos Médicos*") has been developing a number of clinical guidelines; among these, and in the specific area of rare diseases, three guidelines were issued in 2012, which refer, specifically, to the diagnosis and follow-up of Cystic Fibrosis and Pulmonary Hypertension.

Furthermore, the national coordinator of Orphanet-Portugal has been a participant and member of the steering group of *EuroGentest* (and *EuroGentest2*), a EU-funded Network of Excellence, which has developed guidelines and supports the certification and/or accreditation of genetic laboratories, and has taken important steps towards organising and harmonising external quality assurance schemes in genetic testing. He has also closely collaborated, leading several work groups, with EHDN and International Huntington Association for the review of the predictive guidelines and the development of PGD guidelines for Huntington disease. He also participated in the OECD expert group that defined the OECD Guidelines for Quality Assurance in Molecular Genetic Testing³⁵¹, led the process of defining the EMQN BP Guidelines for the Molecular Genetic Testing in the SCAs (dominant ataxias)³⁵², and collaborated for the EMQN BP Guidelines for Molecular Genetic Testing of Huntington Disease (still being finalised).

Training and education

There is no formal programme in this area, but some medicine faculties have lectures on rare diseases and information resources (such as Orphanet), and much work is done in high-schools and by patient organisations and health services.

A Professional Master's Course in Genetic Counselling was initiated at the University of Porto. This two-year post-graduation course is an innovative initiative in Portugal for professionals with diverse clinical backgrounds, including clinical psychologists, nurses and others. This full-time programme encompasses bioethics, clinical and genetic epidemiology, genetic counselling principles and techniques, clinical psychology, research methodologies and clinical rotations, as well as one-year training in a recognised medical genetics service and a research project, with special emphasis on rare diseases.

Some patient associations also organise one-day receptions for medical students, so that they are made aware of rare diseases and rare disease patients.

National rare disease events in 2012

The Portuguese Alliance *APADR*, in collaboration with Orphanet-Portugal, organised a conference to mark Rare Disease Day in 2012. Many patients, relatives, patient associations' representatives, industry representatives, policy makers and health authorities, health professionals and researchers, including several members of the

³⁵⁰ www.linharara.pt

³⁵¹ www.oecd.org/dataoecd/43/6/38839788.pdf

³⁵² www.eurogentest.org/uploads/1283847353000/SCABestPracticeGuidelines-WebsiteVersion.pdf

Scientific Advisory Board of Orphanet-Portugal were present at this event. The conference included presentations of Orphanet tools and activities.

On 20 April 2012, the Orphanet-Portugal team organised a national meeting on rare diseases and orphan medicinal products. This event was part of the DNA Day 2012 and was preceded by the 1st meeting of the National Advisory Board of the Orphanet-Portugal. The topics of the main meeting included: the current status of the Portuguese Rare Disease Plan, the future Reference Centres and Networks for Rare Diseases and Cards for Persons with a Rare Disease, as well as the current status of legislation and regulation of genetic testing and its quality, including the licencing, certification and accreditation of genetic laboratories.

Other events included: Lysosomal Disorders Day conference (28 May 2012), International Day of Ataxias event (22 September 2012), Solidarity Dinner for the International Day of Amyotrophic Lateral Sclerosis (21 June 2012), events for the European Week for Hemochromatosis (7-10 June 2012), events for the International Day of Osteogenesis Imperfecta (6 May 2012), 3rd Symposium of the Study Group of Rare Diseases of the Portuguese Society of Internal Medicine (12-13 October 2012), Annual Meeting of the Portuguese Society of Human Genetics (22-24 November 2012), Symposium on Rare Diseases of the Metabolism (Lisbon, 14 December 2012).

Hosted rare disease events in 2012

Amongst the rare disease related events announced in *Orphanews Europe* in 2012 was: the First International Primary Immunodeficiencies Congress (IPIC), (Estoril, 7-8 November 2013).

Research activities and E-Rare partnership

National research activities

The Foundation for Science and Technology ("*Fundação para a Ciência e Tecnologia*" - *FCT*) runs several programmes to fund research on rare diseases. In 2012, *FCT* funded scientific projects in a total amount of € 583,000.

Participation in European research projects

Portugal participates, or has participated, in the following European rare disease research projects: CLINIGENE, EPOKS, Euro-WILSON, EUR-Ush, PPPT- MJD, SPATAX, EURAMY, EUROCARE CF, EuroGentest-2, EVI-GENORET, INTREALL, LEISHMED, MMR-RELATED CANCER, NEUPROCF, PEROXISOMES, POLYALA, RHORCOD, SAFE, PHGEN, RDCONNECT, STRONG, RIBERMOV and SIOPEN-R-NET.

In 2012, *INSA* participated in ten Research & Development projects on rare diseases, namely the haemoglobinopathies, lysosomal storage diseases, muscular dystrophies, cis-irruption (genomic) disorders and genetic dyslipidaemia. *INSA* also points out its participation in the EUCERD Joint Action, and as member of the ERA-Net on Rare Diseases (E-Rare-2) project.

E-Rare

Portugal, represented by *FCT* and *DGS*, joined the E-Rare-2 Consortium in 2009. However, in December 2012, *DGS* was replaced by *INSA* in this Consortium. During 2012 *FCT* has funded research projects in the amount of €342,000. Portugal joined the 4th Joint Transnational Call in 2012 with Portuguese teams participating in 2 out of the 11 research projects.

IRDiRC

Portuguese funding agencies have not yet committed funding to the *IRDiRC*, however the through the E-Rare Group of Funder, Portugal will be represented at the *IRDiRC* as of the end of 2012.

Orphan medicinal products

In Portugal, regulation of orphan medicinal products is the responsibility of *INFARMED*. A partnership has been established in 2010 between *INFARMED* and ORPHANET-Portugal for a monthly update on all orphan medicinal products, already approved and available in the country.

Following legislation establishing the access of patients to therapies involving diseases with enzymatic deficit, *INSA* coordinates and further authorizes these pharmacological treatments. In 2012, the delivery of enzyme replacement therapy amounted to € 47.5 million. A list of enzymatic diseases, which benefit from free of charge treatment in public hospitals, is also available.

Orphan medicinal product committee

There is no such Committee in Portugal.

Orphan medicinal product incentives

Presently *INFARMED* is not aware of the existence of any specific incentives.

Orphan medicinal product market availability situation

A list of all orphan medicinal products available in Portugal is published at the ORPHANET-Portugal entry site. This data is provided and regularly updated by *INFARMED*.³⁵³

Orphan medicinal product pricing policy

Orphan medicinal product pricing policy falls under the responsibility of the Ministry of Health.

Orphan medicinal product reimbursement policy

There are no specific provisions in place for the reimbursement of orphan medicinal products. All Portuguese citizens are covered by the National Health Service. The investment of the NHS in orphan medicinal products between January and November 2012 exceeded € 63 million, which represents 6.5 % of the total consumption of medicines in hospitals. It should be noted that there was an increase of 16.8 % in this group of medicinal products, as compared to the same period of 2011.³⁵⁴

However, there are special programmes in place to facilitate access to growth hormone therapy and enzymatic therapy.

Other initiatives to improve access to orphan medicinal products

A Special Use Authorisation (*SUA*) procedure is in place to provide access to certain orphan medicinal products. If an orphan medicinal product is not marketed in Portugal, the treating hospital can request a special authorisation from *INFARMED*; if the use is approved, the hospital is directly supplied by the manufacturer and there is no co-payment from the patient.³⁵⁵

Other therapies for rare diseases

There are no other initiatives for improving access to other therapies for rare diseases.

Orphan devices

Under the Directive for Medical Devices, there is no specific regulation for this kind of devices. Instead, there is the possibility of issuing an exceptional authorisation, for the specific utilisation of certain devices, for which the conformity assessment procedure, so as to obtain CE marking, has not yet been completed.

In addition, regarding diagnostic tests for rare diseases, these are usually considered as 'in-house tests' because they are manufactured and used only within the same health institution and on the premises of their manufacture, or used on premises in the immediate vicinity, without having been transferred to another legal entity.

Specialised social services

Respite care services exist in the public, private and social sectors, and patients must pay for some services. Other respite facilities are run by patient organisations and some projects have been established with public support.

In a general way, all patients with rare disease, and depending on their level of functional ability, have access to the same benefits, as any other citizen in the same situation of dependency.

RARISSIMAS has two multidisciplinary centres, which provide clinical care and therapies to patients and families with rare diseases. There are some therapeutic recreational initiatives organised by hospitals with the support of public or private organisations, which are paid through public and private funding; many programmes are organised by several patient organisations, such as the Portuguese Association for Paramyloidosis. There are some projects to help the integration of patients in daily life, and this offer will hopefully improve under the National Plan for Rare Diseases. Some other patient associations organise respite camps.

³⁵³ <http://www.orpha.net/national/PT-PT/index/lista-de-medicamentos-órfãos-disponíveis-em-portugal/>

³⁵⁴ http://www.INFARMED.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ANALISE_MENSAL_MERCADO/ANALISE_MERCADO_MEDICAMENTOS_CHNM/2012/Rel_ConsumoMedicamentos%20em%20Meio%20Hospitalar_201211.pdf

³⁵⁵ EMINET – Initial investigation to access the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner (2011), p 57

1.22 ROMANIA

Definition of a rare disease

Stakeholders in Romania accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

On 29 February 2008, the Romanian Ministry of Health and the country's National Alliance for Rare Diseases (RONARD) signed an accord to form a partnership ("Rare Diseases, a priority for health care in Romania) in order to instate a national plan for rare diseases, following work which started in August 2007 to develop a National Plan, and a National Conference on Rare Diseases in November 2007 on the theme of "Rare diseases: From evaluation of needs to establishing priorities".

A member from the Ministry and from the National Alliance for Rare Diseases (RONARD) were appointed to work together to review the national plan which was developed by rare disease stakeholders and presented to the government at the end of 2007, with the aim of creating an estimate of funding and resources required for each element of the plan. An expert team, including geneticists, paediatricians, endocrinologists, pneumologists, cardiologists, haematologists, informatics specialists, public policy experts and other specialists will be gathered to help evaluate the plan and develop a cost analysis for each item. The country's 2008 health budget was then to be readjusted to include funding for various elements of the rare disease plan.

An official decision of the Romanian Government³⁵⁶ (26 March 2008) stipulated the necessity of various national health programmes in Romania, including a two-year health programme for rare diseases to be funded by the state, covering the diagnosis of rare diseases, the medical treatment of rare diseases and the establishment of several registries linked to specific rare diseases, and rare diseases in general. This "national programme for haemophilia, thalassaemia and other rare diseases" came into force in June 2008 and in reality covers some aspects of health care for rare diseases, but the coverage is limited and does not include all rare diseases and all aspects of health care provision for rare diseases. A budget is currently dedicated to this Programme (Order 1591 /1110/ 30 December 2010 - MH / National Health Security). A working document has been developed with a timeline for implementing specific elements of the programme, which seeks to improve access to information; establish an adequate strategy for ensuring prevention, diagnosis, treatment and rehabilitation services; create a national registry; stimulate research; create rare disease training initiatives for professionals from various fields; and collaborate with various EU and international organisations.

In August 2009, a National Committee for Rare Diseases (composed of professionals and representatives of patient associations) was established involving the Ministries of Health, Education, and Labour, as well as the National Medicine Agency, the Authority of People with Disabilities and the Child Welfare Authority. The main aim of this Committee in 2009-2010 was to elaborate the Romanian National Plan for Rare Diseases. The activities of this committee include government decisions for coordination, guidance and control of services for rare disease patients, including social integration.

The National Programme for diagnosis and treatment for rare diseases is currently coordinated in its methodology by the Commission of Genetics of Ministry of Health, under supervision of Commission of Rare Diseases of Ministry of Health.

Interventions are already put in place for the following purposes:

1. Specific medication assurance:

- a. Prophylaxis and treatment of hemorrhagic events for hemophilic patients and iron chelators for thalassaemic patients
- b. Treatment of patients with:
 - i. Multiple sclerosis
 - ii. Pulmonary Hypertension (PHT)
 - iii. Mucoviscidosis
 - iv. Degenerative neurological disorders
 - v. Miastenia gravis
 - vi. Osteogenesis imperfecta
 - vii. Fabry disease
 - viii. Pompe disease
 - ix. Tirozinemia

³⁵⁶ <http://www.ms.ro/?pag=133>

- x. Bulous epidermolysis
 - xi. Prader Willi syndrome
 - xii. Mucopolysaccharidosis type I and type II
 - xiii. Congenital Afibrinogenemia
 - xiv. Congenital primary immunodeficiency
 - xv. Spinal amyotrophy
 - xvi. Hemophilia
 - xvii. Thalassemia
2. Interventions for early diagnosis and management of spinal amyotrophy and muscular dystrophy (Duchenne and Becker) – coordinating Clinical Pediatric Hospital “Prof. Dr. Al. Obreja” Bucharest, and in second step several hospitals in different towns from Romania;
 3. Interventions for assurance of dietetic food for patients with phenylketonuria;
 4. Intervention for establishing of National Registry for Rare Diseases.

During 2011, the Ministry of Health Rare Diseases Operative Commission was founded (ASC nr. 1132/11.04.2011), coordinated by the National Committee for Rare Diseases. It is involved directly in elaborating and executing of the decisions of the National Committee for Rare Diseases. A Rare Disease Commission has also been created at the University of Medicine and Pharmacy in collaboration with the Member States Rare Diseases Commission. The objectives were to:

- Develop formal address via which committees of the Social Fund can supply data for national programs developed by National House of Health Insurance to Establish a National Registry for Rare Diseases;
- Establish in 2012 an official website within the working groups to disseminate information and requirements formulated at the EU Commission for National Rare Diseases Committee;
- Develop treatment programs according to Directive no. 2011/24/UE European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross border healthcare.

The National Committee for RD met five times in 2012 with the representatives of the Health Ministry to discuss to discuss the government's decisions in order to support the further development of a RD national plan (NP) and national strategy (NS) for the next period of time. The meetings prioritised the areas and actions of intervention in the field of RD, such as, the harmonisation of European and national criteria for establishing centers of expertise at the national/regional level and permanent monitoring and assessment of pathways for patients from contact with the help lines to integration into society.

At the request of the Ministry of Health - Romania, RONARD (Romanian National Alliance for Rare Diseases) has carried out an impact study for implementation of the National Plan for RD in Romania and a strategy proposal to be included in the National Strategy for Health 2014-2020.

During the last four years the National Health Programme for diagnosis and treatment for rare diseases included more patients affected by rare diseases and, so far, 17 rare diseases were included in the program funded and supported by Romanian Ministry of Health. In spite of worldwide economic crisis Romania tried to maintain the same level of funding for RD as in 2011

Centres of expertise

To date, centres of expertise are functioning in Romania, but they are not officially recognised / labeled as centres of expertise. Expertise has been developed around the medical Universities and National Institutes for Health and currently many rare diseases are diagnosed, treated and followed-up.

The criteria and the designation procedure for centres of expertise have been provided in the National Plan for RD, using the EUCERD Recommendations on Quality Criteria for Centres of Expertise adapted to the situation in Romania. A national policy for establishing centres of expertise is not yet clearly stated. An Expert Advisory Committee is established and waiting for the confirmation of Ministry of Health. This Committee will select the criteria, define the policy in the country and organise the national competition for expertise centres.

The number of total national/regional centres of expertise is still debatable based on population size. Following the competition the Centres of Expertise designed will participate in the future European Reference Network.

Currently the genetic diagnosis of rare diseases is carried out in Medical Genetics Centres based in university hospitals.

Expert care is currently provided by many different centres, including: National Institutes of Oncology (Trestioreanu – Bucharest and Chiricuta - Cluj Napoca), Institute of Cerebrovascular diseases (Bucharest), Heart Institute (Cluj), National Institute of Endocrinology (Parhon - Bucharest), National Institute for Mother and Child

(Alfred Rusescu - Bucharest), National Institute for Research and Development "Victor Babes (Bucharest), Fundeni Clinical Institute (Bucharest), etc. In addition, in major Romanian medical centres (Bucharest, Iasi, Constanta, Cluj, Timisoara, Targu Mures) there is a programme in place for the diagnosis of foetal anomalies which also aims to improve care during pregnancy and diagnosis of possible genetic disorders.

A network for Pulmonary Hypertension (PHT) has been composed, including the following following institutes: Institute of Cardiovascular Diseases "CC Iliescu" (Bucharest), Pneumology Hospital (Iasi), Hospital "Victor Babes" (Timisoara), Heart Institute (Cluj) Institute of Cardiovascular Diseases and Transplantation - Pediatric Cardiology Clinic (Targu Mures), Children's Emergency Hospital "Louis Turcanu" (Timisoara), Heart Centre - Cardiovascular Surgery Clinic (Cluj), Department of Paediatric Cardiology (Bucharest).

In addition, many university hospitals are centres of expertise for several specialities, including care for patients with rare diseases. Many national institutes/regional university hospitals serve as tertiary care centres for patients with rare diseases. An extension of expertise to improve its geographical distribution is a provision of the working document of the National Plan currently under consideration. An outline for a system of centres of expertise has been proposed in the National Plan for Rare Diseases based on a network of centres at national, regional and county level by category of disease.

The Operative Commission of Rare Disease founded by the Ministry of Health Rare Disease Commission, will establish a network of Expertise Centres, with specialised laboratories for diagnosing and follow-up rare diseases in University Centres. These centres will include not only genetic laboratories, but all laboratories and facilities needed for the diagnosis and follow-up of the patients with rare diseases, gathered around specialised medical teams involved in this domain. On 29 November 2011 the Ministry of Health Operative Commission of Rare Diseases held a meeting in order to establish the criteria for centres of expertise and networks of these centres in Romania. The university centres were identified by the Commission and documentation was elaborated to be sent to these centres in order to begin the implementation of criteria for centres of expertise for Rare Diseases. In this perspective, the main university centres identified were: Bucharest, Iasi, Cluj, Timisoara, Craiova, Targu Mures. The methodology for the identification of centres of expertise affiliated to "Carol Davila" University of Medicine and Pharmacy Bucharest was discussed, as was the accreditation of these centres in field of rare diseases proposed.

A Pilot Reference Center for Rare Diseases "NoRo" was opened on 28 June 2011 in Zalau, made possible through the project "Norwegian - Romanian (NoRo) Partnership for Progress in Rare Diseases" (2009-2011) with financial support from the Norwegian Cooperation Programme for sustainable economic development in Romania. The project involves 11 partners: Romanian Prader Willi Association (main applicant), Norwegian Prader Willi Association, Frambu - Norwegian Center for Rare Diseases, Ministry Health Romania, The Norwegian Health Ministry, City Hall Zalau, County Council Salaj, Acasa Foundation, "St. Family" Greek Catholic Church Zalau, Romanian National Alliance for Rare Diseases, Romanian Medical Genetics Society and Medical University "Victor Babes" Timisoara. The Minister of Health has allocated a financial support for the new Pilot Centre, amounting to €80,000. The centre offers information concerning RD and through the helpline they refer patients to the specialists involved in the field.

Registries

A national rare disease registry is one of initiatives proposed for inclusion in a national plan for rare diseases. An official decision of the Romanian Government³⁵⁷ of 26 March 2008 stipulates that National Registries should be established and maintained for cardio-vascular diseases (including congenital anomalies), cancers, diabetes mellitus, haemophilia, thalassaemia, psychiatric diseases as well as a National Registry for rare diseases. However, although the Health Ministry plans to organise a national registry for RD but there is not yet a national committee dedicated to dealing with registries and no public financial resources are allocated so far.

Rare diseases included in National Health Programmes or who benefit from free treatment have national registries, but not according with international criteria for drawing up RD registries. In Romania there are some patients' registries in the field of RD but they do not obey all the conditions requested for a registry (National Registry of Haemophilia, the National Registry of Primary Immunodeficiency, the National Registry of Infant Diabetes Mellitus, the National Registry of Thalassaemia, the National Registry of Cystic Fibrosis, the National Registry for Pulmonary Hypertension, the National Registry for Hyperparathyroidism, the National Registry for Acromegaly, and the National Registry of Neuromuscular Diseases; The National Registry of congenital Hypothyroidism and National Registry of Neuroendocrine tumours are under development).

³⁵⁷<http://www.ms.ro/?pag=133>

The Ministry of Health Rare Diseases Operative Commission has established a plan for a National Registry of Rare Diseases based on databases of centres of expertise from each University Centre, able to cover the entire country. The classification of rare diseases is scheduled to be improved in Romania: currently rare diseases are listed in a range of National Programmes apart from that for rare diseases, such as the Oncology Programme, Metabolic Diseases Programme, and Neurological Programme. The centres of expertise will be involved in this activity.

The Meeting of Ministry of Health Operative Commission of Rare Diseases held on 29 November 2011 in Bucharest proposed a common registry of Rare Diseases to be implemented in every Centre of Expertise based on the existing database for different rare diseases. The deadline for establishing a National Registry of Rare Diseases is for 2013. This registry will include common data file identification, a type of program that is included each type of disease tracking centre for each patient (data developed on existing programs out National Health Insurance Agency). The inclusion of new specialities with activity in the field of rare diseases was also discussed, also, in order to extend the present nomenclature of rare diseases.

Romania contributes to the following European registries: EBAR (European Biliary Atresia Registry), EUROCARE CF (European Cystic Fibrosis Registry) and EUTOS (European Treatment and Outcome Study for Chronic Myeloid Leukemia).

Neonatal screening policy

Some 200,000 babies are born every year in Romania. According to national health policy a newborn screening program for phenylketonuria (PKU) and congenital hypothyroidism (CHT) is mandatory. The screening is performed in 4 public medical centers throughout the country (Bucharest, Iasi, Cluj-Napoca and Timisoara). However, despite the screening programme, some tests are not available nationwide due to logistic and resource problems and no addition has been made to the panel of diseases tested. In 2010 efforts were made via the Health Programme at local level in order to generalise and improve the organisation of neonatal screening for these two disorders, as well as to introduce screening for other diseases. The 2010 health policy improved the management of screening for PKU and CHT at local level, reaching 80% coverage for newborns. Tests for newborn screening are provided by private clinics/laboratories at full cost, and screening for other conditions (i.e. hearing loss) can be carried out in the framework of research programmes.

The current policy for prenatal screening and diagnosis in Romania includes a national programme for all pregnant women over age 35 at conception offering tests free of charge. Biochemical screening, ultrasound and CVS/amniocentesis are performed in 6 public medical centres throughout the country. Prenatal screening/diagnosis is also offered to all pregnant women independently of maternal age with costs eligible to be covered by national health insurance. At this time, prenatal testing procedures are invasive and performed for the most common clinically significant foetal aneuploidies. Prenatal diagnosis is also used to determine whether a foetus has a rare monogenic disorder. Usually, for a foetus at increased risk for rare monogenic diseases, CVS/amniocentesis and DNA isolation are performed in many public or private clinics. Then, the DNA samples are sent abroad for molecular diagnosis of rare monogenic diseases (sequencing for entire gene or selected exons).

In 2012 Romania joined contributed to the efforts aimed at the preparation of European guidelines on diagnostic tests or population screening (in the scope of the Tender on New Born Screening European Network of Experts) respecting national decisions and competences.

Genetic testing

Genetic testing is available in Romania but is not covered in the National Programme for Rare Diseases. Physicians specialising in genetics only are allowed to provide genetic counselling, and testing is usually performed in the scope of specific projects.

Genetic testing can be carried out before birth (via amniocentesis or chorionic villus samples) and after birth and includes molecular or cytogenetic tests. DNA tests, sexual chromatin, conventional karyotype and FISH analysis are offered by public or private laboratories. Such genetic testing laboratories are placed in university centres (Bucharest, Cluj, Craiova, Iasi, Oradea, Targu-Mures and Timisoara). Some of them are officially recognised and accredited at national level as having specific expertise in the field. Private laboratories offer a variety of modern molecular tests for purchase. Genetic testing includes cytogenetic and molecular investigations, such as, standard karyotype, FISH, DNA molecular test (MLPA, QF-PCR, array CGH, targeted sequencing).

Genetic testing is recommended by a physician (i.e. obstetrician, paediatrician, medical geneticist, haematologist and oncologist). Usually the results of genetic tests are interpreted by a medical geneticist who can also offer the genetic counselling. In Romania the health insurance does not cover the costs of genetic

tests. But some genetic tests are free of charge for children who are enrolled in national health programme for birth defects. Other times, the patients could be enrolled in research programmes or non-profit humanitarian programmes that genetic tests are available for free.

Romania, as is the case of other European countries, cannot provide genetic tests for all disorders: other specific tests unavailable nationally are available abroad. Form S2 for Health Care Abroad/E112 offers is used in these cases. Diagnostic tests are registered as available in Romania for 31 genes and an estimated 45 diseases in the Orphanet database³⁵⁸.

There are no national practice guidelines for genetic testing yet, but guidelines are being developed. Professional organisations (Romanian Society of Medical Genetics) and other NGOs are working on these guidelines based on European recommendations.

National alliances of patient organisations and patient representation

RONARD (The Romanian National Alliance for Rare Diseases) is the national alliance for rare diseases founded and initiated by the Romanian Prader Willi Association (RPWA) which organises meetings and information services.

In 2012 the alliance organised:

- Meetings of the National Committee for RD with the representatives of the Health Ministry to discuss the priorities of the National Plan for RD and how to organise the competition for the designation of centres of expertise;
- The Rare Disease Day in Bucharest and helped with the organisation in major university centres;
- The EUCERD Joint Action Workshop – Guiding Principles for Specialised Social Services;
- Helpline for the patients with RD;
- Lectures in the field of RD for the patients, as well as for the specialists (they are accredited for doing this);
- The patient organisations component of the alliance organised activities in their field and they are supported by the Romanian National Alliance for RD (ANBRaRo).
- Moreover, the Alliance will organise the Europlan Conference in 2013.

Several new organisations for patients with rare diseases have been established and joined the national alliance.

The NoRo project (2009-2011) has been developed in partnership with the Ministry of Health and funded by the Norwegian Programme of Cooperation with Romania and its goals are derived from the National Plan for Rare Diseases. Rare disease patient representatives from Romanian National Alliance for Rare Diseases and the professionals involved in NoRo project continue to organise the meetings of the National Committee for Rare Diseases in order to update and advocate for the implementation of the National Plan for Rare Diseases in Romania.

In addition, many other former or recently patients associations, as Muscular Dystrophy Association, Congenital Heart Disease Foundation, PKU Life Romania Association, and Romanian Association for Haemophilia, National Association Myasthenia Gravis, Romanian Network of Hereditary Angioedema, Romanian Society for Multiple Sclerosis, Mini Debra Association for Patients with Epidermolysis Bullosa, Romanian Association for Patients with Neuroendocrine Tumours, Pulmonary Hypertension Patients Association, have intense activities in the field of implementation of National Plan.

Sources of information on rare diseases and national help lines

Orphanet activity in Romania

Since 2004 there is a dedicated Orphanet team in Romania, currently hosted by Universitatea de Medicina si Farmacie “Gr T Popa”, Iasi. This team was designated as the official Orphanet team for Romania by the Ministry of Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. An Orphanet country site was launched in 2012.

Official information centre for rare diseases

The Romanian Prader Willi Association established an Information Centre for Rare Genetic Diseases in 2005³⁵⁹, providing information for patients and medical experts, encouraging the exchange of information and experiences between people affected by the same rare disease, and providing counselling and support groups

³⁵⁸ Information extracted from the Orphanet database (December 2012).

³⁵⁹ http://www.apwromania.ro/oamenirari/ghid_servicii_en/index.html

as well as training. The activities are financed by different projects and the service is accredited by the Ministry of Labour. Through the NoRo project a virtual platform for rare diseases has been developed (www.edubolirare.ro), both for information and authorised trainings of different professionals, including personal assistants, including videoconference facilities which can be used for provision of information, counselling and training to patients.

Help line

The NoRo helpline (080 080 1111), was initiated by the Romanian Prader Willi Association/ RONARD, which continues to provide and fund this Ministry of Labour accredited service. The helpline is also subsidised by the Ministry of Labour. In 2011 the helpline was improved by introducing Orphacodes in the call information management software. In addition, a caller profile analysis was carried out, together with the other members of the European Network of Help Lines for Rare Diseases. Legal attestation has been granted assuring that the service operates according to the Romanian legislation of data protection and privacy. The helpline is part of the European Network of Helplines organised by Eurordis, together with the helpline provided by the Romanian Association for Myasthenia Gravis.

Other patient organisations in Romania also run specific helplines, including the Romanian Society of Rare Diseases provides an official contact via the e-mail address rarediseasesromania@yahoo.com and work on a website was underway in the second half of year. This site provides official news.

Other sources of information on rare diseases

The site <http://bolirare.ro/> provides some information on rare and genetic diseases, in Romanian. A monthly magazine for patients (Rare people and rare diseases) is available. A trimestrial scientific journal in cooperation with RSHG and Medical University of Timisoara entitled the "Romanian Journal of Rare Diseases³⁶⁰" was also launched in 2010. This publication is the international official journal of the National Committee for Rare Diseases, founded and initiated as part of the NoRo project ("The Norwegian-Romanian Partnership (NoRo) for progress in Rare Diseases") of the Romanian Prader Willi Association funded by the Norwegian Government through a grant of the Norwegian Cooperation Programme for growth and sustainable development in Romania. The Romanian Prader Willi Association also produces the publication "Rare People and Rare Diseases" for patients and the public. Other sources of information include lectures by specialists in the field.

Good practice guidelines

The Operative Commission of Rare Diseases will work to create guidelines for rare diseases in Romania. Every speciality establishes clinical practice guidelines, which published in the Official Romanian Monitor, the official legislative journal under the authority of the Ministry of Health. Good practice guidelines are produced in some university centres based on key publications of professional associations in the field.

The Romanian Society of Medical Genetics is working to elaborate best practice guidelines for rare diseases in Romania according to European regulations.

Training and education initiatives

The Ministry of Health Commission for Rare Diseases foresees a workplan for training sessions and conferences involving all expertise centres, starting in 2012, and lectures on rare diseases will be centralised on a specific website.

One of the most important missions of the National Commission of Rare Diseases is to determine a relevant analysis of rare diseases in Romania, as part of university education, because the introduction of this subject in university curriculum is a necessity determined by continuous adaptation to socio-economic environment. In other words, the quality and specificity of academic and university environment is influenced by continuous society dynamics. Considering the scientific and medical aspects of rare diseases, it is necessary to include such topics in the university curricula for students of Universities of Medicine and Pharmacy all over the country; the graduate courses and doctoral theses focused on this topic should include the latest information based on field research at the highest level on rare diseases. Due to a high level of academic training information adaptive to continuous medical changes, Faculty of Medicine graduates would acquire not only the necessary information in order to perform their medical activities at the highest level, but also the professional skills that will allow their rapid integration under conditions of competition.

³⁶⁰ www.rjrd.ro

Currently, rare diseases are included in optional/ facultative lectures covering rare diseases for medical students, as well as post graduate lectures on Medical/ Clinical Genetics are organised in major university centres. An increase in the trend of rare diseases being discussed in such contexts has been recently observed.

Leaflets with information concerning major genetic disorders are available for parents in some Medical Genetics Centres.

In some Medical Genetics Centres, after receiving genetic counselling, the parents receive a Medical Genetics Certificate that contains detailed information about the affected child, diagnosis, Orphanet information and patients' associations (with contact details).

In 2010 Romanian Prader Willi Association/ RONARD was accredited for organising training/ educative courses in the field of rare diseases and these courses started in 2011. This initiative includes new services for patients with rare diseases in the context of the NoRo project, such as a virtual platform for rare diseases in Romania (eUniversity)³⁶¹ which contains information for the general public and training modules. The training modules are authorised by the Ministry of Work and Education and targeted at different professionals involved in rare diseases (personal assistants, social workers, psychologists, special education teachers) and a training course for medical doctors: "Management of the rare diseases" accredited by the Doctors Collegium for CME. A training calendar for patients has been elaborated and the training courses started with the opening in 2011 of the Pilot Reference Centre for Rare Diseases "NoRo". The various training courses inform all kinds of specialists in rare diseases through help-line telephone line and specialised web pages. Those activities are supported by the Romanian Society of Medical Genetics (SRGM), through a partnership between RONARD and SRGM. Training sessions are held in Timisoara, Bucharest, and Iasi, thanks to RONARD and the Save the Children organisation.

National rare disease events in 2012

The Romanian National Alliance for Rare Diseases has marked Rare Disease Day with many events since 2008. The alliance coordinates efforts and collects the information about the campaign events organised by the member organisations. In 2012, Rare Disease Day was an opportune event to support efforts to advocate at the Ministry of Health level for the Romanian National Plan for Rare Diseases to be included in the National Strategy for Public Health and to keep maintain collaborations with other Ministries (ex. Education and Research, Work and Social Affairs). The Romanian National Alliance for Rare Diseases is organising a meeting of the National Committee for Rare Diseases in Bucharest on 16 February 2012 to this effect. On 17 February 2012 a round table was organised in Bucharest, focusing on the topics of the national plan, the framework for organising the centres of expertise, the quality criteria for centres of expertise, the possibilities for organising and accrediting the centres of expertise in Romania, and Romania's participation in European Reference Networks for Rare Diseases.

Member organisations held events to mark the day in Bucharest, Timisoara, Cluj-Napoca, Iasi, Zalau, Targu Mures and Oradea. These events were for patients and their families, for specialists involved in the management of rare diseases and for the general public, and took the form of marches, conferences, workshops, PlayDecide sessions, ability workshops, lessons on rare diseases in schools, and artistic events.

The Orphanet Romania team helped organise the annual conference of the Romania Society of Medical Genetics.

Hosted rare disease events in 2012

The EUCERD Joint Action workshop on Specialised Social Services was hosted in Zalau, Romania (6-7 December 2012).

Research activities and E-Rare partnership

National research activities

Funding is currently available from some sources in Romania, although there are no specific programmes for rare diseases research in Romania. Research projects dedicated to rare diseases are included in the same category with other research projects. In 2012 there was a general call for projects (non-rare disease specific). There are currently no other fund-raising initiatives for rare disease research in Romania.

Participation in European research projects

Romania contributes/contributed to the EUROPEAN LEUKEMIA NET European research project and the European Network for Study of Adrenal Tumours - ENS@T.

³⁶¹ www.edubolirare.ro

E-Rare

Romania is not currently a partner of the E-Rare consortium.

IRDiRC

Romanian funding agencies have not yet committed financing to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

No specific activity reported.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product availability

From 1 January 2007, date at which Romania became an EU Member State, all medicinal products were required to obtain new authorisations according to EU standards: this created significant delay in the importation of certain orphan medicinal products. As a consequence of the creation of the National Plan for Rare Diseases, the Ministry of Public Health enlarged coverage of orphan medicinal products from July 2008 onwards in their health programme.

The list of orphan medicinal products available/commercialised in Romania and free of charge through the National Health Programme is available on the website of the Romanian National Medicines' Agency³⁶² and includes: Aldurazyme, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyf, Gliolan, Glivec, Increlex, Inovelon, Litak, Lysodren, Myozyme, Naglazyme, Nexavar, Onsenal, Orfadin, Pedeia, PhotoBarr, Prialta, Replagal, Revatio, Revlimid, Savene, Siklos, Soliris, Somavert, Sprycel, Sutent, Tassigna, Thalidomide Pharmion, Thelin, Torisel, Tracleer, Trisenox, Ventavis, Volibris, Wilzin, Xagrid, Xyrem, Yondelis, Zavesca.

Orphan medicinal product pricing policy

There is national debate for regulation in this area.

Orphan medicinal product reimbursement policy

The National Programme for Rare Diseases provides for the reimbursement of 47 orphan medicinal products in Romania.

Other initiatives to improve access to orphan medicinal products

In Romania there are several ways of accessing orphan medicinal products via Order N° 962/2006 for approval of the application of art. 699, paragraph (1) of Law N° 95/2006 including: compassionate use of drugs for a certain patient (in the case where the drug already has marketing authorisation); compassionate use of drugs for a group of patients with an invalidating disease, either chronic or serious, or a disease considered to be life-threatening (the provision of a centrally authorised product); the off-label use of drugs. However, the public payer will not always reimburse the orphan medicinal product provided.

Many companies (i.e. Genzyme, Novartis) use humanitarian programs, sponsorship or partnership with medical societies in order to provide the orphan medicinal products, like Tassigna, Evoltra, Fabryzyme, Myozyme, and others. This way was a successful manner to give access of the patients to some orphan medicinal products. Other ways include the enrolment of patients in clinical trials for orphan medicinal products. Doctors have to prescribe the compassionate / off-label drugs and follow-up the patients.

Other therapies for rare diseases

No information reported yet.

Orphan devices

No information reported yet.

³⁶² <http://www.anm.ro/ /Lista%20medicamentelor%20orfane%20valide%20in%20Romania.xls>

Specialised social services

There are currently no respite care services available in Romania. Therapeutic and rehabilitation programmes (not specifically targeted at rare disease patients) are available and patients generally do not have to pay: these programmes are provided by patient organisations and governmental institutions, and some by private companies. RPWA in partnership with ACASA Foundation has initiated a programme for “patient groups rehabilitation and training programmes” as part of the NoRo project. Patient organisations also provide social services such as centres for integration through occupational therapy: these activities are funded through projects, and if the patient organisation provides an accredited service, subventions are available from the Ministry of Labour. Patients with chronic disabilities can apply for special aid compensation and funding for a personal assistant and/or reduced taxes when necessary.

A complex type of specialised social service called Resources Centre for RD has been developed in Romania by the Romanian Prader Willi Association-NoRo Center, which represents a combination of information, social and medical services. The Centre was established with Norwegian funding through Norwegian Cooperation Program and it is working for 1 year and a half, supported partly by the local and national authorities. The service includes training courses, information and guidance services, provision of information about social services, documentation and research. Daily support therapies, medical and psychological consultations are also provided by NoRo center. This service also aims to create a bridge between patients/families and all the stakeholders involved in patient care, such as medical services, rehabilitation and therapeutic services, social services and social support authorities, education professionals and other professionals directly working with RD patients.

1.23. SLOVAK REPUBLIC

Definition of a rare disease

Stakeholders in Slovak Republic accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

A working group was established in January 2011 at the Ministry of Health to work on a strategy for improving health care for patients with rare diseases. This strategy includes the basic concepts for the plan, and was adopted in April 2012 by the Ministry of Health, before being adopted by the Government of the Slovak Republic on 24 October 2012. The Interministerial Committee for the National Plan will organise a Europlan national conference including specialists in the field in February 2013 and also a National conference on 28 February 2013. There is hope of adopting the Plan by the end of 2013.

Centres of expertise

There is currently no official policy concerning centres of expertise for rare diseases and no official centres of expertise for rare diseases in Slovak Republic. Health care for several rare diseases is centralised mainly at the Departments of Clinical Genetics (12 in the country), the Centre for metabolic diseases (1 in the country), and in several specialised outpatient clinics for metabolism or few types of rare diseases, as well as in cooperation with some research laboratories of Slovak Academy of Science. Several specialised and centralised departments would be appointed as centres of expertise in the near future (e.g. oncogenetics, hereditary metabolic diseases, neuromuscular disorders, arterial pulmonary hypertension, haemophilia, alkaptonuria).

Registries

At present, there is no national committee dedicated to dealing with registries and no national rare disease registry, however the future National Plan for Rare Diseases will look at ways of collecting patient data. National health registries are financed by Ministry of Health of the Slovak Republic. The National Health Information Center (NCZI) is the operator of most national health registries. Of these the following registries are for rare diseases: the National registry for congenital disorders (established in 2011), the National registry for congenital heart defects (established in 1992), the National cancer registry (established in 1976 including rare cancers), the National child diabetes mellitus and neonatal diabetes registry (established in 1986).

The NCZI provides data from the new registry focused at the monogenic forms of diabetes. The registry has been launched in 2008 based upon the data produced by the DIABGENE Laboratory at the Institute

of Experimental Endocrinology, Slovak Academy of Sciences. In 2011 the National child hypertension registry was established as sub register of cardiovascular registry.

There are also several disease-specific registries managed outside of the NCZI (i.e. clinical registry of haemophilia). Slovak patients are registered also in international registries as REaDy – REgister of muscular dystrophies (<http://ready.registry.cz/>). Currently, the database registers a total of 54 patients from Slovakia, one of which is a woman.

The Slovak Republic contributes to the EUROCARE CF and RARECARE registry.

Neonatal screening policy

Neonatal screening (NBS) policy has been officially established by the Ministry of Health in the Slovak Republic. Screening is in place since 1985 for congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, and cystic fibrosis. Screening is provided in one central National Newborn Screening Centre, in coordination with three regional Recall Centres providing definitive diagnostic procedures and continuous management of confirmed cases. MS/MS technology has been introduced into selective screening. In addition to the screened diseases every newborn/infant is screened for hearing disorders, hip dislocation and the majority of newborns (more than 90%) are screened immediately after birth by means of USG for somatic malformations (CNS, cardiol, obstructive uropathy, etc.) although this is not an official governmental policy. In 2012 a document on newborn screening was adopted, expanding the panel of screened diseases from 4 to 13, to include hyperphenylalaninemia (HPA), leucinosi (MSUD), MCAD, LCHAD, VLCAD, CPT I., CPT II.A, CACT, glutaric aciduria type I (GA I), and isovaleric aciduria (IVA).

The National Newborn Screening Centre is a member of EUNENBS (European Union Network of Experts on Newborn Screening).

Genetic testing

As a small country, the Slovak Republic does not have a large number of laboratories for genetic testing. Genetic testing is organised by the Departments of Clinical Genetics (12 in the country), specialised genetic outpatient clinics or specialised Departments of Clinical Oncogenetics (2 in the country). There are 5 bigger and several smaller DNA laboratories which perform or provide molecular diagnostics for around 350 monogenic mendelian disorders. There are currently no reference laboratories in Slovak Republic.

The Slovak Republic has also participated in elaboration of several international “Best Practice Guidelines”, e.g. “Molecular Genetic Diagnosis of Maturity – onset Diabetes of the Young”.

Specific provisions for the reimbursement of tests are not yet in place and genetic testing for non-medical reasons is paid for by the person requesting the test. Slovak Society of Medical Genetics and health insurance companies are now developing new system of reimbursement of genetic testing. Genetic testing also takes place abroad, mainly in the Czech Republic.

Diagnostic tests are registered in the Orphanet database for 53 genes and an estimated 52 diseases³⁶³.

National alliances of patient organisations and patient representation

The Slovak Rare Diseases Alliance was established at their first constitutive meeting held in Bratislava in Slovakia on 12 December 2011 and is composed of 12 patient organisations out of the 17 related to rare diseases in the country. Close cooperation with the National Working Group for Rare Diseases in Slovakia and the National Coordinator of Orphanet Slovakia and other professionals was also established. The main activities and goals of the Slovak Rare Disease Alliance were presented at the First Slovak Conference on Rare Diseases, held in Bratislava on 29 February 2012. The fundamental challenge for the Slovak Rare Disease Alliance is to raise public awareness for the conditions of people with rare diseases and to participate in the formation of National Plan for Rare Diseases. Slovakia joins the growing number of countries across Europe forming national alliances for rare diseases. Such collaborations bring together individual rare disease patient groups to work together on the common goals of obtaining diagnostics, research, care, treatment and social services for rare disease patients. The Alliance also publishes a newsletter.

There are no public funding schemes for patient organisations in Slovak Republic. Some patient organisations are members of the NR OZP SR (National Disability Council in Slovak Republic). A patient representative is present in the rare disease strategy working group.

³⁶³ Data extracted from the Orphanet database in December 2012.

Sources of information on rare diseases and national help lines

Orphanet activities in the Slovak Republic

Since 2006 there is a dedicated Orphanet team in the Slovak Republic, hosted before 2010 by the Institute of Molecular Physiology and Genetics in Bratislava. In 2010, in the context of the Joint Action Orphanet Europe, the Ministry of Health designated the 2nd Department of Paediatrics of the University Children's Hospital Bratislava as the official Orphanet team for Slovak Republic. This team is engaged in collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team launched in 2011 the Orphanet Slovakia national website^{364, 365}. Part of the Orphanet Encyclopedia was translated to Slovak language and this initial set of 150 rare disease descriptions is now available on the Orphanet Slovakia website. The Slovak Orphanet team initiated and organised the First Slovak Conference on Rare Diseases to commemorate the 2012 Rare Disease Day. The Conference was organised in close cooperation with EUCERD representative and Slovak National Alliance of Rare Disease Patient Groups.

Official information centre for rare diseases

There is no official information centre for rare diseases other than Orphanet in Slovak Republic.

Help line

There is currently no dedicated help line for rare diseases at the moment.

Other sources of information on rare diseases

Information sources on rare diseases are mostly run by non-governmental organisations with a few projects supported by the state and its municipality. One well developed information source is internet page of Slovak Rare Disease Alliance. More used sources of information for professionals in clinical genetics are the websites OMIM (Online Mendelian Inheritance in Man), GeneTests, and many other web sites for another medical specialities.

Good practice guidelines

Good practice guidelines have been developed for cystic fibrosis, maturity-onset diabetes of the young, Wilson disease and haemophilia, as well as for new born screening. Some molecular genetics laboratories in Slovakia have been participating in the EMQN programme and EQA KRAS programme. The Slovak Republic participated in elaboration of the international Best Practice Guidelines for Molecular Genetic Diagnosis of Maturity-onset Diabetes of the Young. National guidelines for genetic testing were developed and adopted by the Slovak Society of Medical Genetics (SSLG) in June 2012. SSLG, oncogenetics laboratories and Association of Health Insurance Companies developed guideline for diagnostics and clinical management of HBOC.

Training and education initiatives

Currently, there are no training or education initiatives organised systematically in the field of rare diseases.

National rare disease events 2012

To mark Rare Diseases Day, the first Slovak Conference of Rare Diseases³⁶⁶, organised by Orphanet Slovakia, was held on 29 February 2012: the conference was held under the auspices of the Minister of Health of the Slovak Republic and the Deans of the Comenius University Medical School and Faculty of Pharmacy in Bratislava. The aim of the conference was to raise awareness about diseases that most people will not know of, as well as to improve access to treatment. Together 150 invited participants attended from health care providers, patient organisations, scientific institutions, public insurance companies and social affairs institutions. The English abstracts from presentations and posters were published in the official journal of the Faculty of Pharmacy, Comenius University in Bratislava and are freely available³⁶⁷.

In addition, a press conference/round table on the subject of orphan drugs³⁶⁸ was held with experts in the field on 20 February 2012 in Bratislava with the aim of providing information on the subject of orphan drugs, addressing the question of why orphan drugs are so expensive and considering the Slovak Republic's

³⁶⁴ <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/> www.zriedkave-choroby.sk

³⁶⁵ <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/>

³⁶⁶ www.zriedkavechoroby.sk

³⁶⁷ <http://www.degruyter.com/view/j/afpuc.2012.vii.issue-0/issue-files/afpuc.2012.vii.issue-0.xml>

³⁶⁸ <http://zbierka.sk/news/default.aspx?itemid=1202200230>

approach to rare diseases. The first three sections were concerned with recent European actions in the field followed by invited talks on the role of centres of expertise and cross-border collaboration. The third part of the conference will concentrated on social, health and community policy. A poster section was also organised to map the country's resources in diagnosis, treatment and patient care.

Izakovic's Memorial is an annual conference organised in Slovak Republic by the Slovak Society of Medical Genetics, related to genetic and rare diseases. The 23rd conference had international attendance and was held in Bratislava on September 2012 welcoming over 200 participants. The main topics included Genetics and Biology of Neurological Disorders, Cytogenetics, Oncogenetics, Prenatal Diagnostics, Clinical Genetics, Molecular Pathology, Syndromology, Trends and Research.

Hosted rare disease events 2012

Amongst the hosted events announced in *OrphaNews Europe* in 2012 was the 6th International Workshop on Alkaptonuria (Piestany, 1-2 November 2012).

Research activities and E-Rare partnership

National research activities

Currently there are no specific programmes for rare disease research in Slovak Republic.

Participation in European research projects

Teams from the Slovak Republic participate, or have participated, in European rare disease research projects including: ANTEPRION and NM4TB.

E-Rare

Slovak Republic is not currently a partner of the E-Rare Project.

IRDiRC

Slovak funding agencies do not currently commit funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

The Slovak Republic does not have a national orphan medicinal product committee, and currently does not have a representative at the COMP neither in EUnetHTA. The Slovak Ministry of Health is responsible for system of pricing and reimbursement of all drugs as well as orphan medicinal products.

Orphan medicinal product incentives

To attract orphan medicinal products manufactures to launch the Slovak market better information about the patients with rare diseases is needed to be able to estimate the real need in this relatively small country. Formation of national strategy/plan might help to solve this problem.

Orphan medicinal product market availability situation

SUKL, the State Institute for Drug Control, is the regulatory body in the Slovak Republic responsible for the regulation and surveillance of human medicinal products and medical devices, including orphan medicinal products. The data about the adverse events is submitted to the European database of suspected adverse drug reactions.

The reimbursement level is set in a national process named "categorisation". The "categorisation committee" established at the Ministry of Health is responsible for pricing and reimbursement.

All orphan medicinal products registered at EU level are available in the Slovak Republic. Directly available on the Slovak market at the end of 2012 were 25 orphan medicinal products: Myozyme, Aldurazyme, Naglazyme, Zavesca, Kuvan, Ventavis, Revolade, Nplate, Firazyf, Volibris, Tracleer, Revatio, Somavert³⁶⁹), Increlex, Litak, Nexavar, Sprycel, Tassigna, Torisel, Revlimid, Lysodren, Vidaza, Inovelon, Exjade, Tobi podhaler. The rest can be provided at named-patient basis. For this the physician has to submit a special application at the Ministry of Health. The information about the amount of OMP distributed at named-patient basis is not published for now.

³⁶⁹ Orphan status withdrawn in 2012.

Orphan medicinal product pricing policy

No specific information reported.

Orphan medicinal product reimbursement policy

At the end of the year 2011 Slovak Ministry of Health introduced a monthly update of “categorisation list”, thus increasing the possibilities for all pharmaceutical companies as well as orphan medicinal product pharma companies to launch their products. The “categorisation list” is published every month.

At the end of 2012 out of the 25 orphan medicinal products, 6 orphan medicinal products require patients’ participation towards costs (Myozyme plc ifo 10x50 mg, plc ifo 25x50 mg, Tobi podhaler plv icd 224x28 mg, Firazyr sol inj 1x3ml, Inovelon tbl flm 50x200 mg, tbl flm 50x400 mg). The highest copayment was for Tobi podhaler plv icd (€529.84, which means 21.68% of the total price). The average copayment is 4.62% of the total price (0.87 – 21.86%).The orphan medicinal products are distributed mainly through pharmacies as well as on a centre basis, depending on the reimbursement category which is also set in the “categorisation list”³⁷⁰.

Other initiatives to improve access to orphan medicinal products

Thanks to the participation in the REaDy – REgister of muscular dystrophies, 2 patients with Duchenne muscular dystrophy were involved in the clinical trial. Because of unavailability of centres of expertise, the treatment was given in Czech Republic, in Brno.

Orphan devices

No specific information reported.

Other therapies for rare diseases

No specific information reported.

Specialised social services

Care services, both government-run and private, are available in Slovak Republic and partial or full reimbursement is available (depending on certain criteria). Therapeutic programmes such as spa stays are available and paid mainly through private health insurance.

1.24. SLOVENIA

Definition of a rare disease

Stakeholders in Slovenia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of not more than 5 in 10 000 individuals. The same definition is also accepted in The Work Plan for Rare Diseases.

National plan/strategy for rare diseases and related actions

In 2012 a national plan for rare diseases was accepted by the Health Council and the next steps will be to elaborate an action plan and its implementation, as well as to identify funding. The Work Plan for Rare Diseases³⁷¹ is designed to serve as a roadmap until 2020 and is qualified as “... an opportunity for better coordination of efforts of all partners involved, establishing health care that will be comprehensive, accessible, timely and patient-focused”. The major objectives of the plan centre around the identification and monitoring of rare diseases; improving early diagnosis and access to appropriate medical treatments; mechanisms to improve an integrated approach to rare diseases; and improving access to information for patients, the general public, and professionals. Amongst identified actions include the establishment of a national registry for rare diseases; establishment of national reference centres integrated with international networks; examining cross-

³⁷⁰Foltánová, T. / Konečný, M. / Hlavatá, A. / Štěpánková, K. / Cisárik, Orphan drugs used for treatment in Paediatric patients in the Slovak Republic, <http://www.degruyter.com/view/j/afpuc.2012.lix.issue-0/issue-files/afpuc.2012.lix.issue-0.xml>

³⁷¹http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podroczju_redkih_bolezni.pdf

border cooperation for genetic testing and other services; introducing a system of evidence-based clinical guidelines; defining orphan drug policy and developing decision guidelines for competent authorities; identifying additional funding sources for orphan drugs; establishing an umbrella organisation of patient groups; and establishing a national centre for rare diseases in the country.

Centres of expertise

There are no official centres of expertise in Slovenia, but the majority of patients with rare diseases in Slovenia are evaluated centrally at the University Medical Centre Ljubljana where there is an efficient system for the referral of genetic, endocrine, metabolic, and neurodegenerative disorders, amongst others. In addition to this, there is a Centre for Fabry disease in Slovenj Gradec. The establishment of centres of expertise is foreseen in the national plan for rare diseases.

Registries

There is currently no national registry for rare diseases in Slovenia. A new Healthcare Databases Act, which sanctions the establishment of national registries, is under preparation, and the inclusion of registries in the area of rare diseases is expected.

Slovenia contributes to the EUROCARE CF European registry and RARECARE registry.

Neonatal screening policy

Neonatal screening is available for phenylketonuria and congenital hypothyroidism. A screening policy is also in place for hearing impairments and developmental dislocation of the hip.

Genetic testing

Genetic testing is offered to patients when there is an indication to perform such tests recognised by a medical specialist. While there are no formally established reference centres in Slovenia, the Institute of Medical Genetics at the University Medical Centre in Ljubljana is the tertiary institution in this area. There are no specific national guidelines regulating genetic testing, those that are deemed necessary are financed by the Health Insurance Institute of Slovenia. In case a specific test not being available in Slovenia, there is a procedure in place, through which patients can obtain approval for reimbursement of genetic testing performed abroad.

Diagnostic tests are registered as available in Slovenia for 62 genes and an estimated 73 diseases in the Orphanet database³⁷².

National alliances of patient organisations and patient representation

There is currently no national alliance of rare disease patient organisations in Slovenia. Patient organisations are financed through different sources: this may include funding from the government/public sector and the private sector (private sponsorships and donations). The Ministry of Health financially supports some programmes within patient organisations through calls for project proposals: the aims of these calls vary.

The role of patient organisations is recognised in national plan. Patient organisation representatives are usually consulted concerning legislative proposals and in some cases are included in the process of drafting legislation. Patient organisation representatives do not usually receive financial support in order to attend these meetings.

Sources of information on rare diseases and national help lines

Orphanet activities in Slovenia

Since 2006 there is a dedicated Orphanet team in Slovenia, currently hosted by the Institute of Medical Genetics at the University Medical Centre Ljubljana. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was designated by the Ministry of Health in 2010 as the official Orphanet team in Slovenia. The team launched in 2011 the Orphanet Slovenia national website³⁷³.

³⁷² Information extracted from the Orphanet database (December 2012).

³⁷³ <http://www.orpha.net/national/SI-SL/index/domov/>

Official information centre for rare diseases

There is no official information centre for rare diseases in Slovenia other than Orphanet at the moment. Establishment of national contact point for patients and professionals to get some extensive information on rare diseases diagnosis and treatment is foreseen. This will be the first action to be implemented in the Work Plan for Rare Diseases. There are on-going negotiations with the stakeholders.

Help line

There is currently no information help line for rare diseases in Slovenia.

Other sources of information on rare diseases

Information on rare diseases is available on some institutions' web sites, and web sites run by patient organisations.

Best practice clinical guidelines

The national clinical guidelines are available for the 4 inborn errors of metabolism which are treated with enzyme replacement therapy (Fabry disease, Pompe disease, MPS II and VI).

Training and education initiatives

No specific activity reported.

National rare disease events in 2012

On 29 February 2012 a press conference was organised by Ministry of Health as a way to raise awareness of rare diseases to mark Rare Disease Day 2012. The event was also the opportunity to inform the general public on rare diseases and to improve cooperation between patients and medical professions for a better quality of life. On the same day gathering of different stakeholders on the field of rare diseases (patient organisations, health care providers, medical doctors, ministry representatives, representatives of local community, press) was carried out by one of patient organisations.

Hosted rare disease events in 2012

No specific information reported.

Research activities and E-Rare partnership

National research activities

The Slovenian Research Agency is a government body which awards grants for research. Although not specifically aimed at rare diseases, in the past rare disease topics have been given research grants.

Participation in European projects

Slovenian teams participate, or have participated, in European rare disease research projects including: CONTICANET, EMSA-SG, MYELINET, PNSEURONET and SARS/FLU VACCINE, PARENT Joint Action, European Fabry Registry Advisory Board.

E-Rare

Slovenia is not currently a partner of the E-Rare project.

IRDiRC

Slovenian funding agencies have not yet committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

In Slovenia, orphan medicinal products are included in public funding in the same manner as any other drug. A decision on their financing from public funds is adopted by a commission of experts in the field of medicine and pharmacy within the Health Insurance Institute of Slovenia. Additionally a Strategic Council for Drugs operates within the Ministry of Health. It is responsible for policy and funding availability of medicinal products - particularly expensive drugs, including orphan medicinal products. In 2012 The Health Insurance Institute of Slovenia put on positive hospital list both orphan medicinal products: clofarabine (Evoltra) and busulfan (Busilvex) that were in 2011 covered by additional funding. The Strategic Council for Drugs in 2012 provided

additional government budget funds of 794.537,00 € to finance two orphan medicinal products: eculizumab (Soliris) for 2 patients and idrusulfase (Elaprase) for 1 patient.

Orphan medicinal product incentives

In Slovenia, there are several measures concerning national incentives for orphan medicinal products according to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, including “reduced fees for marketing authorisation procedure (if the centralised procedure was not followed)³⁷⁴.”

Orphan medicinal product market availability situation

The orphan medicinal products launched on the market up to the end of 2012 were: Adcetris, Afintor, Arzerra, Busilvex, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Glivec, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedeia, Peyona, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tassigna, Tepadina, Thalidomide, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Vpriv, Wilzin, Xyrem, Yondelis, Zavesca.

Orphan medicinal product pricing policy

Pricing of orphan medicinal products is subject to the same procedure as other medicinal products, which are financed from public funds. Determination of maximum prices is the responsibility of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP), whereas the Health Insurance Institute of Slovenia negotiates prices that are lower than those set by JAZMP. The latter sets the maximum prices taking into account those set in a selection of EU countries (Germany, France and Austria).

Orphan medicinal product reimbursement policy

In Slovenia, one of the criteria for including a drug among those covered by health insurance is an “ethical criteria” which applies in particular to severe and rare diseases: this has a positive influence on the accessibility of drugs for rare diseases patients.

All orphan medicinal products are covered mainly by compulsory health insurance and some partly by complementary health insurance, without the need for any co-payment by the patient.

The expenditure for orphan medicinal products increased by 44,9 % from 2010 to 2012, whereas total expenditure for other drugs was in 2012 lower in comparison to 2010 due to systematic price regulation.

Other initiatives to improve access to orphan medicinal products

In Slovenia, there are several measures concerning national incentives for orphan medicinal products according to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, including “permission to use medicines labelled in any EU language with stickers in Slovenian language; [and] negotiation on drug prices.³⁷⁵”

Other therapies for rare diseases

In Slovenia other therapies for rare diseases are also available, for example: implantation of subdermal pump for treatment of epilepsy, surgical corrections of rare inborn heart defects, cranial synostosis, inborn facial defects and transplantation of hematopoietic stem cells.

Orphan devices

No specific information reported.

Specialised social services

Some respite care services are available in Slovenia for patients with disabilities, and are provided by governmental and non-governmental organisations with either government or private financing. Some services are available in Slovenia for patients with disabilities. Therapeutic recreational programmes are available for patients with disabilities in Slovenia, and are provided by governmental and non-governmental organisations with government and private financing. Services are in place promoting the social integration of patients with disabilities in the workplace: most activities are provided through government institutions.

³⁷⁴ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

³⁷⁵ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

1.25. SPAIN

Definition of a rare disease

Spain accepts the definition of the "Community Action Programme on Rare Diseases (1999-2003)" of a rare, minority, orphan or uncommon diseases as a life-threatening or chronically debilitating diseases with a prevalence of less than 5 cases per 10 000 inhabitants.

National plan/strategies for rare diseases and related actions

The first national initiative taken in relation to rare diseases was the creation of the Toxic Oil Syndrome Research Centre (Centro de Investigación sobre el Síndrome del Aceite Tóxico, CISAT), of the Carlos III Health Institute (Instituto de Salud Carlos III, ISCIII), in 1996, with the mission of coordinating the treatment of, and research on, Toxic Oil Syndrome. As of the year 2000, the Government progressively became involved in care and research regarding rare diseases, and extended the activities of the CISAT, which by Ministerial Order of 27 December 2001 became the Toxic Oil Syndrome and Rare Diseases Research Centre (Centro de Investigación del Síndrome del Aceite Tóxico y Enfermedades Raras, CISATER). One of the initiatives undertaken by the CISATER led to the creation of the first Spanish Rare Diseases Information System (Sistema de Información de rare diseases, in Spanish, SIERE). The first collaborative study on rare diseases patients' needs was then developed between IMSERSO (*Instituto de Mayores y Servicios Sociales* – Institute of the Elderly and Social Services) and CISATER. In 2003, the Carlos III Health Institute created by Ministerial Order of 7 November, the Institute of Rare Disease (IIER) to be worth at the structure of Health system³⁷⁶. The tasks assigned to the aforementioned centre were those of maintaining and supporting the development of research and of implementing a National Research Programme in that field. At the same time, a National Ethics Committee for rare diseases was set up in December 2004 with the participation of the IIER.

In 2006, the Centre for Biomedical Network Research on Rare Diseases (CIBERER) was created in order to act as a reference, coordinate and foster research on rare diseases in Spain. The CIBERER is one of the nine consortia of research created by the ISCIII to encourage the research of excellence in biomedicine and sciences inside the NHS. The CIBERER is oriented towards the development and implementation of cooperative research in the field of rare diseases, favouring basic, clinical and epidemiological biomedical research, placing special emphasis on transferring the research from the laboratory to the patient's bedside and scientifically responding to the questions that arise from the interaction between physician and patient³⁷⁷. In 2012, the ISCIII has reinforced the Institute of Rare Diseases Research (IIER) with a new Human Genetic Brand, which is developing rare diseases research initiatives in iPCs development, searching new orphan drugs and looking for new diagnosis tests.

A centre for rare diseases in Burgos, *Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias de Burgos* (CREER) -"State Reference Centre for Rare Diseases Patients and their Families"- was inaugurated on 30 September 2009 by the Spanish Ministry of Health, Social Services and Equality. This is a centre of expertise with the following missions, amongst others: coordination, research, innovation, professional training, dissemination of information and awareness raising and support to other Spanish organisations. CREER can accommodate up to 60 people distributed in 12 family flats and additional day care places with the aim of providing integral care following the recommendations of the EU. CREER will also play an important role anticipating respite programmes for the families, promoting the mutual knowledge and exchange of experiences between patients and families and providing information training concerning welfare policy, as well as social and health care. All areas are coordinated to feed into one another: new knowledge is applied to improve care and quality of life of people with rare diseases and their families.

Rare Diseases Strategy of the Spanish National Health System (2009)

In 2008 the Spanish Senate launched an official declaration after reaching a general agreement by all political parties where a strong recommendation regarding rare diseases actions was addressed to the Government of Spain. At the beginning of 2008, the Government began to work on a National Strategy on Rare Diseases creating two committees (a Technical Committee made up of 15 scientific societies and 3 patient organisations and an Institutional Committee made up of the representatives appointed by the Health Departments of the Autonomous Communities") which developed the contents of the Strategy. The Rare Diseases Strategy of the Spanish National Health System was approved by the Interterritorial Council of the Spanish NHS on 3 June

³⁷⁶ <http://www.boe.es/boe/dias/2003/11/14/pdfs/A40101-40103.pdf>

³⁷⁷ <http://www.boe.es/boe/dias/2011/02/22/pdfs/BOE-A-2011-3539.pdf>

2009³⁷⁸. The elements defined in the Spanish strategy allow for the fulfilment of the recommendations established by the European Council Recommendation on an Action in the Field of Rare Diseases. The Rare Diseases Strategy of the Spanish National Health System represents a consensus between the Ministry of Health, Social Services and Equality, the Carlos III Health Institute, Autonomous Communities, patient organisations, scientific societies and experts.

The Strategy is structured into three parts. The first part, 'General aspects', includes the justification, the purposes of the Strategy (its mission, principles, the values it inspires), the definition of rare diseases and their situation in Spain. In addition it covers their historical development and epidemiological situation. Finally, it sets out the strategy development methodology. The second part, 'Development of strategic lines', sets out the objectives and recommendations. The participants of the Strategy decided, by consensus, to establish the following strategic lines: information on rare diseases, prevention and early detection, healthcare, therapies, integrated health and social care, research and education/training. The third part, Monitoring and Evaluation, sets out the process that makes it possible to monitor the proposed actions.

The strategic lines are broken down into 13 general and 37 specific objectives, with their respective technical recommendations and monitoring and evaluation indicators. In short, this document aims, on the basis of available information/evidence, to establish a set of objectives and recommendations to be achieved which, in a realistic manner and according to the available resources and the areas of competence of the Autonomous Communities, will help improve the quality of interventions and outcomes in the field of rare diseases.

Given the decentralised health administration of Spain in the Regional Governments (regional governments), the Strategy will act as a framework and a set of recommendations for the different regions, who will in turn be in charge of implementation. Funds are allocated through a call for proposals opened to the Regional Governments in order to facilitate the implementation of the Strategy. The Strategy for Rare Diseases as well as any other related measures or actions aimed at rare diseases are included in the Spanish National Health Budget.

A Europlan National Conference on Rare Diseases was held in Burgos at the *Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias de Burgos* (CREER) on 4-5 November 2010 in the context of the Europlan project. The conference was attended by a range of stakeholders who all had the opportunity to evaluate the degree of implementation of the different Europlan Recommendations in Spain and discuss these issues during the conference. The final report is available online³⁷⁹.

Indicators have been defined for the evaluation of the Strategy and it was evaluated in 2012. This assessment focused mainly on the implementation of the Strategy over the first two years, although it is too soon to measure health results, this process could help to update recommendations and objectives. The results, and consultation with the Stakeholders, could help update the Strategy. As a result of the evaluation, it can be confirmed that the Strategy has been implemented in the majority of the Regional Governments (RG). In addition, 70.7 % of the specific objectives evaluated have been achieved by more than 50% of the RG.

The main achievements have been, amongst others: the establishment of the National Registry for Rare Diseases, availability of an inventory of services and tests of prenatal diagnosis and derivation protocols for pregnant women at risk or foetal RD, to raise awareness and recognition of rare diseases, and to promote socio-health care and research for children under three with rare diseases. Moreover, the evaluation has also showed that it is necessary to implement actions aimed at collecting and disseminating information and resources available on rare diseases, to increase training of primary care professionals on suspected diagnosis of rare diseases and to establish adequate criteria for referral, to improve the availability of basic health information to the teaching staff that attends children with rare diseases, to develop initiatives of joint coordination and planning for the adaptation of jobs and for the management of the reintegration and continued employment of family members of persons affected by rare diseases, to carry out initiatives to facilitate keeping persons with rare diseases in their surroundings such as home care services, home hospitalisation, day centres, and so on, to develop integration activities in the community (leisure activities) for those with rare diseases, and to promote participation of patients associations in participation-decision bodies in the area of health of the Regional Governments.

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government expects to raise knowledge and awareness for rare conditions,

³⁷⁸ <http://www.msc.es/organizacion/sns/planCalidadSNS/docs/RareDiseases.pdf>

³⁷⁹ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_spain_%20europlan.pdf

and establish stronger ties of mutual support. The operation will focus on the health, research and social perspective of rare diseases³⁸⁰.

Regional initiatives

Before the launch of the Rare Diseases Strategy of the Spanish National Health System in 2009, some regional initiatives had already been put in place. The Regional Government of Andalusia (*Junta de Andalucía*) created a genetics plan, the *Plan de Genética de Andalucía 2006-2010*, which, in turn, led to the creation of the *Plan de Atención a Personas Afectadas por ER 2008-2012*, a plan concerning care for people affected by rare diseases.

The Extremadura Autonomous Community approved in December 2010 its Plan Integral de Enfermedades Raras 2010-2014 based on general recommendations from Europe and the Spanish National Strategy. The Health Department of the Regional Government of Catalonia (*Generalitat de Catalunya*) approved an Order for the creation of an Advisory Commission on rare diseases in 2009, with the aim of enhancing the implementation of specific health policies aimed at these pathologies, some of which are already included in Catalonia's different existing master plans (on integrated health and social care, mental health, oncology, etc.).

Also, the Regional Government of País Vasco has developed a *Plan de acción de la estrategia de enfermedades raras en la comunidad* in 2011 and this region has approved an Order for the creation of an Advisory Commission on Rare Diseases in 2012.

Centres of expertise

The legal base for designating reference centres, departments and units (RCDUs) in Spain is the Spanish National Health Service (SNS) Cohesion and Quality Act (16/2003). It sets out the legal framework for coordination and cooperation between public health authorities in the exercise of their respective functions and defines reference services that require the centralization of cases in a small number of centres for their best management and to guarantee equitable access to high-quality, safe and efficient health care for patients affected by conditions that require highly specialized care.

In Spain, Royal Decree 1302/2006 establishes the procedure and principles for the designation and accreditation of the Reference Centres, Departments and Units (CSUR) of the Spanish NHS. It defines the characteristics to be met by diseases or groups of diseases in order to have a designated CSUR:

- a. Diseases that for their adequate care require preventive, diagnostic and therapeutic techniques, technologies and procedures of a *high level of expertise* requiring experience in their use, which can only be acquired and maintained through certain volumes of activity;
- b. Diseases that require *high technology* for their prevention, diagnosis or treatment and for which, in view of their cost-effectiveness and the available resources, the concentration of a minimum number of cases is required;
- c. *Rare diseases* which, because of their low prevalence, require a concentration of cases for their adequate care, which does not imply the ongoing care of the patient in the reference centre, service or unit, but rather that the latter can act as a support for diagnostic confirmation, the definition of therapeutic strategies and follow-up strategies and as an adviser for the clinical units that usually treat those patients.

The entire procedure for the designation of CSUR is formulated through the CSUR Designation Committee from the Spanish NHS, that was set up in 2006 and it is composed of the representatives from the different Regional Governments, the Ministry of Health, Social Services and Equity, National Transplant Organisation (ONT) and the Healthcare Technologies Assessment Agency and which reports and submits proposals to the Interterritorial Council. The tasks of the Designation Committee are: to study the needs and propose the pathologies or the diagnostic or therapeutic techniques, technologies and procedures for which a CSUR needs to be designated; to propose the procedure for the designation and accreditation of a CSUR and to report on it; to assess the designation applications received and make designation proposals to the Interterritorial Council; to study and propose the renewal/revocation of the designation of CSUR; and to establish the procedure for the referral of users.

Given that it was difficult to deal with all the different areas of specialisation at the same time, work is underway with groups of experts, designated by the Autonomous Communities, the Scientific Societies and the Ministry of Health, Social Services and Equality. These groups are making a proposal of the diseases or procedures for which it is necessary to designate CSUR and the criteria to be met by these in order to be designated as of reference. Since July 2007, the Interterritorial Council has agreed to 46 pathologies or

³⁸⁰ <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

procedures for which it is necessary to designate CSUR in the Spanish NHS, as well as, the criteria that these shall meet to be designated as reference.

Among these pathologies and procedures, all of them of low-prevalence, there are some concerning rare diseases such as the following:

- Reconstruction of the outer ear
- Congenital glaucoma and glaucoma in childhood
- Congenital disorders of eye development (alterations of the eyeball and eyelids)
- Extraocular Tumours during Childhood (Rhabdomyosarcoma)
- Intraocular Tumours during Childhood (Retinoblastoma)
- Penetrating keratoplasty in children
- Children's transplants (kidney, intestine, liver, heart, lung)
- Allogenic transplant in children from hematopoietic parents
- Child Orthopaedics: Orthopaedic treatment in neuromuscular diseases (cerebral palsy, myelomeningocele), congenital malformations (congenital short femur, tibiofibular agenesis), bone dysplasia (imperfect osteogenesis) and great lengthening of members
- Comprehensive care of the neonate with congenital heart disease and children with complex congenital heart disease
- Family heart disease (includes hypertrophic cardiomyopathy).
- Hereditary ataxia and paraplegia
- Paediatric Arrhythmology and Electrophysiology
- Refractory Epilepsy
- Complex Paediatric Neurosurgery

Once the criteria have been agreed a period of CSUR application is opened, and the Regional Governments can present their proposals through the Designation Committee. Once they have been admitted for processing, the audit and accreditation process starts. After the respective accreditation reports have been received, the Designation Committee studies them and submits its proposals for designation, or non-designation, to the Interterritorial Council. The Ministry of Health, Social Services and Equality, at the suggestion of the Designation Committee and with the prior consent of the Interterritorial Council, decides on the designation of the CSUR for a maximum period of 5 years. Before that period has terminated the designation is renewed, provided that the re-evaluation is satisfactory.

Some official centres of expertise for rare diseases have already been designated by this procedure. Up to now, the Interterritorial Council and the Ministry of Health, Social Services and Equality have agreed to designate 177 CSUR for 43 pathologies or procedures, including some related to rare diseases. Around 72 of these CSUR are related to rare diseases.

At the same time, work continues in other areas of specialisation to define all the diseases and procedures, among them those related to rare diseases, which should be carried out in CSUR. Since 2001, FEDER (The Spanish Federation for Rare Diseases) has been working in the CSUR project with regard to rare diseases, by providing professionals to participate in the groups of experts related to rare diseases.

In March, 2013, the Interterritorial Council agreed on 7 new pathologies and procedures for and their specific designation criteria:

- Imported tropical diseases
- Metabolic congenital diseases
- Neuromuscular diseases and rare diseases of motoneuron different to ALS
- Genetic neurocutaneous syndromes (Facomatosis)
- Rare diseases that occur with disorders of movement.
- Amyotrophic lateral sclerosis
- Complex upsets of the autonomic nervous system

Reference services are monitored annually. An information system is in place to report on how the activities performed comply with the designation criteria and meet the procedure and result indicators that were included in the designation criteria. The information system has begun gathering data for 90 reference services that started operation in 2009 and 2010, covering 26 diseases and procedures. The definition of these procedures and result indicators by the corresponding expert groups and units and services designated (agreed by the Interterritorial Council) is very complex, due to the diversity of diseases and procedures, considering that every disease and procedure has its own information system.

Currently, the annual follow-up of 132 CSUR of the NHS is being carried out. These CSUR serve 35 diseases and procedures, and they have been operating in 2009, 2010, 2011 and 2012. Each year collected data and indicators are analysed by professionals from CSUR and expert groups in each area of expertise, and if required, appropriated improvements are introduced.

All information concerning the CSUR project is available for health professionals and patients in the Web of the Ministry of Health, Social Services and Equality (MSSSI).

During 2013 the MSSSI will be involved in the implementation of European Reference Networks (ERN) in the context of the Directive of Cross Border Health Care.

Registries

The Spanish Network of Rare Diseases Research on Epidemiology (REpIER) was created in June 2003 and analysed the existing rare diseases registries in Spain as of 2005. It concluded that the identified registries did not fit the standard criteria for epidemiological surveillance except for those population based registries which were mainly focused on rare cancers. Most of the registries defined as rare diseases registries were hospital case series intended for clinical studies' development. In 2007 the ISCIII decided to start designing a rare diseases national registry at its Institute of Rare Diseases Research (IIER). A Spanish patient's registry for rare diseases including several and different approaches and programmes has been developed and is online as of 2009. The Institute of Rare Diseases Research (IIER), belonging to ISCIII, is currently in charge of this registry. This registry is sustained by government financing at the moment. Since December 2011, a project on the "Spanish Rare Disease Registries Research Network" (an IRDiRC project: see corresponding section) is being carried out and coordinated by IIER; all the Regional Governments are participating in the project. The main objective is to develop the National and Regional registry for rare diseases based on methods for both population-based registries and patient outcomes registries. Industry, patient's organisations, foundations and more than 6 medical societies have signed agreements with the ISCIII to contribute to this national registry and cooperate with the IIER.

In Spain, there are several population based cancer registries which officially report to the International Agency of Research Cancer of the WHO. Since REpIER was put in place, a specific working group was set up for this particular group of rare diseases as well as for congenital malformations. Both groups are working in collaboration with European and international networks (including EUROCAT) and participate in several European projects.

At regional level, Extremadura has run a population-based registry on rare diseases since 2004. Andalusia, Castilla-La Mancha, Murcia, Comunitat Valenciana and Catalonia are taking steps to develop their own.

Spain also contributes to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, EIMD, ESID, EURO-WABB, MOLDIAG-PACA, AIR, SCNIR, EURO CARE CF, ENERCA and TREAT-NMD.

Neonatal screening policy

National neonatal screening is currently in place for phenylketonuria and hypothyroidism. Hypoacusia is included in all Autonomous Communities. Nevertheless, the neonatal screening programme offer differs greatly among different Spanish Autonomous Communities: 14 of them and the 2 Autonomous cities included cystic fibrosis and, 6 congenital adrenal hyperplasia, 4 sickle cell disease, 2 biotinidasa deficiency and 4 galactosemia. In addition, 9 Regional Governments and 2 Autonomous cities have extended the newborn screening programme by Tandem Mass Spectrometry. Efforts are being made to standardise the offer at national level.

A working group with representatives from the Ministry of Health, and the Regional health services, reviewed scientific evidence and will produce a report and recommendations about population screening programs for the National Health System³⁸¹. A previous study on the situation of newborn screening programmes in Spain, the *Informe sobre la situación de los programas de cribado neonatal en España* was carried out in 2007 by the Public Health Commission of the Interterritorial Council of the Spanish NHS³⁸². The aim of the study was to strengthen and promote the early identification and treatment of affected persons, thereby avoiding neurological damage and reducing morbidity, mortality and possible disabilities associated with certain diseases through timely interventions. Accordingly, the new recommendations of child health

³⁸¹ A document on screening in general (neonatal and cancer screening) was elaborated in 2010 : "Documento marco sobre cribado poblacional" elaborated by the Comisión de Salud Pública del Consejo Interterritorial del SNS (2010) (Committee for Public Health of the Interterritorial Council of the National Health System) (2010)

³⁸² "Report on the neonatal screening programmes situation in Spain" elaborated by the Comisión de Salud Pública del Consejo Interterritorial del SNS (2007) (Committee for Public Health of the Interterritorial Council of the National Health System) (2007)

programmes stress the importance of the early detection of diseases and at-risk groups, as well as the supervision of the growth and overall development of the child, which enables the identification by paediatricians and other health professionals of warning signs and of the early detection of developmental disorders, which can be part of the symptoms associated with several rare diseases.

Also, one Spanish Technology Health Assessment Agency has been developing criteria for the cost-effectiveness of a neonatal screening programme using Tandem Mass Spectrometry³⁸³.

Genetic testing

The Spanish Law 14/2007 on Biomedical Research, which considers genetic testing in research and care, stipulates that when carrying out a genetic analysis for health purposes “the interested party must be guaranteed appropriate genetic counselling”. Since the early 1970s genetic counselling in Spain has been provided by specific hospital services, although in the case of inherited metabolic diseases that task was usually carried out by the actual paediatrician or by the diagnostic laboratory. Usually the genetic services offer cytogenetic, molecular genetic and biochemical genetic tests (in the case of inherited metabolic diseases) as well as genetic counselling. These services are provided by health professionals: medical staff, highly qualified non-medical staff, nursing staff and laboratory technicians; and the genetic counselling is usually done by highly qualified staff. The basic training of these health professionals varies, and they may well come from different specialties.

In Spain, genetic diagnostics and counselling are disciplines which, initially, were associated with activities in hospital environments. In the Spanish NHS those activities are currently carried out by different professionals who have been trained and who have acquired experience in these areas.

As regards patients’ access to genetic testing and counselling, in Spain “referral of patients for genetic testing is nearly exclusive of hospitals and specialised care. It can also be performed for clinical reasons or as part of a research protocol”, according to the conclusions of a study carried out by the Institute for Prospective Technological Studies (IPTA).

The Spanish Law 14/2007 on Biomedical Research defines “genetic testing” as the “procedure to detect the presence or absence of, or change in, one or more segments of genetic material, including indirect tests for the detection of a gene product or other specific metabolite that is primarily indicative of a specific genetic change”. It is estimated that tests are currently available for more than 1000 genetic diseases. Nevertheless, their clinical use has been limited for several reasons. At times there are no external quality assessment services and at others insufficient data is available for their interpretation and validation. But the protocols and guidelines of best practices applicable to each case must always be taken into account, as must the legislative framework in which the genetic testing must be performed, whether for research or in the health system (Spanish Law 14/2007 on Biomedical Research).

At the present time, the MSSSI is working together with Regional Governments and Scientific Societies defining the genetic portfolio of services for the NHS and HTA agencies which are involved in the description of the Spanish map of genetic test offered by the NHS.

Genetic tests for 1521 genes and an estimated 1541 diseases are registered in the Orphanet database³⁸⁴.

National alliances of patient organisations and patient representation

FEDER, the Spanish Rare Disease Federation, was established in 1999 as a non-governmental organisation (NGO). Currently, FEDER with its 190 members is recognised as an umbrella organisation for the 3 million people with rare diseases in Spain and their families. Several services to patients have been developed, funded by public and private, national and regional funds. FEDER has been very active in advocating for an Action Plan in different National Conferences (2005, 2006), as well as participating in the Technical Committee of the Ministry of Health, Social Services and Equality for the development of the National Strategy for Rare Diseases. Apart from this, FEDER is active at European level, present on the EURORDIS board and participating in many European projects at national level. FEDER is a member of the Spanish Committee of Disabled (CERMI) and the Spanish Patients’ Forum and is usually represented at regional level at the Health Councils. Support for patient organisations is provided by private and public (Labour Ministry and Ministry of Health) funds and organisations for patients with disabilities are also supported by the IMSERSO (Ministry of Health, Social Services and Equality).

³⁸³ Paz Valiñas L, Atienza Merino G. Efectividad clínica del cribado neonatal de los errores congénitos del metabolismo mediante espectrometría de masas en tándem. Revisión sistemática. Madrid: Ministerio de Sanidad y Consumo. Avalia-t. Nº 2006/07.

³⁸⁴ Data extracted from Orphanet in December 2012.

FEDER has developed several specific agreements with CREER in order to improve the collaboration and the empowerment of FEDER patient's organisation and has also signed a Framework Agreement with CIBERER.

In 2012, FEDER organised along with the company Fluor the collection of used mobile phones to go towards fundraising for rare diseases.

Other National alliances that in the Technical Committee of the Ministry of Health, Social Services and Equality for the development of the National Strategy for Rare Diseases are the Coalición de Ciudadanos con Enfermedades Crónicas (Alliance of citizens with Chronic Diseases), Federación Española de Enfermedades Neuromusculares (Spanish Federation of Neuromuscular Diseases), and la Federación Española de Fenilcetonuria y Otros Trastornos del Metabolismo (Spanish federation of Phenylketonuria and Other Methabolic Disorders).

Sources of information on rare diseases and national help lines

Orphanet activities in Spain

Since 2002, there is a dedicated Orphanet team in Spain, currently hosted by CIBERER. This team is in charge of collecting data on rare diseases related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was designated by the Ministry for Health, Social Policy and Equality in 2010 as the Orphanet team in Spain. The Orphanet portal is available in Spanish and the national team maintains a national Orphanet Spain website³⁸⁵ in Spanish providing extra socio-educational documentation. CIBERER supports the translation into Spanish of the Orphanet website content and contributes to the site with national data. The Spanish Rare Diseases Registry (IIER - ISCIII) signed an agreement with Orphanet in 2009 in order to use the same rare diseases classification system as Orphanet. In March 2011, Orphanet Spain signed an Agreement with the AEGH by which the Spanish national team will have access to a compiled list of all the laboratories that have registered in the AEGH.

Official information centre for rare diseases

There is no official information centre on rare diseases in Spain other than the services provided by Orphanet which is supported by the Ministry of Economy and Competitiveness.

Help line

FEDER's Service of Information and Orientation (SIO) provides a phone and internet helpline which receives support from the Ministry of Health. The help line is coordinated with specific rare disease info services and provides information on rare diseases, patient management of the disease, experts and consultations, obtaining a diagnosis, access to medicinal products, clinical trials, genetic tests, rehabilitation, publications, guidelines for creating a patient organisation, and information on financial support and respite care. FEDER's help line also provides information to callers from Spanish speaking countries. It also acts as a contact point for experience exchange amongst patients with the same pathology or pathology group. The help line belongs to the European Help Lines Network, led by EURORDIS.

Other sources of information on rare diseases

Other sources of information were developed by rare diseases research networks such as REpIER, INERGEN, GIN; ORGEN, REDEMETH, REC-GEN, etc. They are in different stages of development and some have been recently closed or their information is being transferred to the national registry website. CIBERER also runs a website with information regarding its main lines of research.

FEDER maintains a website with information on rare diseases and certain documentation and runs a specialised helpline for patients and their families and social services professionals, the Information and Support Service (SIO) which has received more than 34462 consultations since 2001, when it was established with the support of the former Social Affairs Ministry. Social, legal, psychological support as well as training is provided to individual patients, associations, professionals (and others) by specialized staff (e.g. five social workers and a biologist). There are two related services: Psychology Service (attended by 3 psychologists) and a legal consultancy attended by 1 lawyer. CREER is working with FEDER and the IIER on a new system to improve the coordination of different competences for providing several types of information on rare diseases. The System of Information for Patients (FEDER Help line) is thus also improved.

³⁸⁵ <http://www.orpha.net/national/ES-ES/index/inicio/>

FEDER also promotes social and sanitary studies on rare diseases such as the 2009 “Estudio ENSERio “Estudio sobre situación de las Necesidades Sociosanitarias de las personas con Enfermedades Raras en España” FEDER, followed up in 2012 by the “Estudio ENSERio 2 “Por un modelo sanitario para la Atención a las personas con Enfermedades Raras en las Comunidades Autónomas”

Good practice guidelines

Since 2000, *IMSERO* (the main Spanish Institution in charge of providing social support for disable patients and families) has also been collaborating with FEDER in order to develop guides for rare diseases families, i.e. Amiotrophic Lateral Sclerosis, Achondroplasia, Familial Spastic Paraparesis and Aniridia, amongst others.

*GuíaSalud*³⁸⁶ is a programme which is supported by the Ministry of Health. Since its first steps in mid-2002 until now, it has been immersed in framework changes within the quality of the NHS Plan. The measures were described in the Quality Plan of 2007, which implicated important changes to objectives, introducing into the work portfolio the development of products, based on scientific evidence, to assist health professionals in decision-making. Several guidelines for specific rare diseases have been developed by *GuíaSalud*, i.e. related to congenital abnormalities or skin care in epidermolysis bullosa and related to congenital hypothyroidism.

CIBERER also collaborates, along with the Spanish Orphanet team, in the revision and transplantation of GP guidelines on rare diseases.

There is also a Health Technology Assessment Agencies network that develops reports concerning specific rare diseases since 2006 (i.e. ataxias, inborn errors of metabolism or genetic tests).

CIBERER has developed a programme aimed at facilitating information to all those interested through guides and brochures on specific illnesses and/or through scientific lectures meant for patients. CIBERER has produced nearly 150 clinical guides on rare diseases since 2007 intended for nurses, general practitioners and clinical specialists. This research centre also organises therapeutic conferences, workshops and seminars in cooperation with other bodies such as patients’ associations. CIBERER is committed to ensuring excellence amongst their scientific laboratories. Most of them are already accredited and some others are in the process of obtaining the best level of standard quality through external validation processes.

An online protocol for the primary care of patients with rare diseases was presented on 18 July 2010 at the national congress of the Spanish Society of Family and Community Medicine (SEMFC) in Valencia. The protocol, *Protocolo Dice de Atención Primaria de Enfermedades Raras (DICE-APER)* was created by SEMFC’s working group on Clinical Genetics and Rare Diseases³⁸⁷, in collaboration with the Institute of Rare Diseases Research Institute, ISCIII, FEDER and CREER. The specific objectives of the protocol are to facilitate the diagnostic process, provide information to patients, improve coordination between primary care and specialised care physicians and render epidemiological data.

The Ethics Committee of the Institute of Rare Diseases Research (IIER) has published a series of guideline documents regarding registries, biobanks, and neonatal screening³⁸⁸. Originally published as separate articles in the Spanish Health Ministry publication *Revista Española de Salud Pública*³⁸⁹, the Ethics Committee has now grouped the guidelines into one document, entitled *Ethical Guidelines for Biomedical Research*, which it has made available in both Spanish and English languages. The guidelines address issues pertaining to creation, organisation, management, consent, privacy, post-mortem data, and ownership, within the context of existing ethical principles and norms, legal provisions, and international practices.

Training and education initiatives

Since 2007 the CIBERER holds an annual scientific meeting where the principal investigators and pre-doctoral/postdoctoral researchers present their recent results in the field of the biology, pathophysiology, clinical research and therapies, and epidemiology in the field of rare diseases.

The Universidad Internacional de Andalucía (UNIA) and the Universidad Pablo de Olavide de Sevilla (UPO) in collaboration with the CIBERER, offers an official Master in ‘Rare Disease Diagnosis and Therapy’ since 2010. In 2012 the third edition took place as well as the program for the fourth edition to be held in 2013.

Other initiatives led by CIBERER are the organisation of training courses on rare diseases.

In 2010 The Ministry of Health, Social Policy and Equality funded 10 projects related to the training and education on rare diseases carried out in different Spanish Regions in 2011 also 10 projects were funded, 3 of them related to training and education.

³⁸⁶ <http://www.guiasalud.es/home.asp>

³⁸⁷ <http://dice-aper.semfc.es/web/index.php>

³⁸⁸ http://www.isciii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf

³⁸⁹ http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm

The Institute of Rare Diseases Research have participated in the two editions of the Summer School of Rare Diseases held in Bulgaria, 2011 and Greece, 2012 respectively. These summer schools are addressed to train to health policy makers from Russia.

Each year FEDER and CREER organise a training school aimed at empowering rare disease patients groups.

National rare disease events in 2012

FEDER has organised various National Conferences on rare diseases and Regional Conferences. Many other rare disease specific patient associations hold their annual meetings where some time is dedicated to comment on general questions concerning rare diseases. Some Medical and Scientific Societies include round table discussions and conferences related to rare diseases in their annual meetings.

Every year, the Spanish Federation of rare diseases (FEDER) celebrates Rare Disease Day, with hundreds of patient organisations organising a wealth of events. In the build up to Rare Disease Day 2012, the Orphanet Spanish team also contacted with all the associations registered in Orphanet asking them to collaborate and obtaining a list of around 20 different events.

Amongst the events in Spain organised to mark the Day included a number of round tables, workshops and exhibitions across Spain, as well as the passing of an act recognising rare disease day in parliament. FEDER also marked the day with an official prize-giving to honour people working in the field.

The Fifth National Rare Disease Congress was organised in October 2012 by the Spanish Rare Diseases Alliance (FEDER) and D'Genes Association in Totana, Murcia. The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year for Rare Diseases at this conference. The objective of this initiative is to raise awareness of rare diseases and to make them more visible to society, as well as to stir the interest of new researchers, health professionals and the industry in order to continue developing treatments and advancing the knowledge of these diseases. At the meeting, the Minister spoke about her commitment to develop a coordinated strategy to tackle rare diseases with a multidisciplinary approach that includes health, social and scientific perspectives.

Hosted rare disease events in 2012

Every two year since 2000, the Royal College of Pharmacists in Seville has organised the International Congress on Orphan Drugs. The last one has been in February, 2013. All stakeholders have participated in this event. Other events announced in *OrphaNews Europe* in 2012 included: BioSpain Conference (Bilbao, 19-21 September 2012), 8th International Congress on Autoimmunity (Granada, 9-13 May 2012), World Pulmonary Hypertension Day-Scientific Symposium (Madrid, 4-5 May 2012) , 2nd Annual Orphan Drug Congress 2012 (Barcelona, 7-8 June 2012).

Research activities and E-Rare partnership

National research activities

In Spain, research related to rare diseases is included in the "*Plan Nacional de Investigación Científica*" (National Plan for Scientific Research), "*Desarrollo e Innovación Tecnológica*" (Development and Technological Innovation) (2008 – 2011), and specifically within the "*Acción Estratégica en Salud*" (Strategic Action on Health [Research]), in which rare diseases constitute one of the most important research subjects. In September 2007, the outlines of the National R&D&I Plan were presented. According to the Ministry of Education and Science, the Public Central Administration increased its investment at a rate of 16% per year starting in 2008 and up to a total expenditure of 2.2% of GDP in 2011, in line with European Union recommendations. This estimate includes the business sector, which will finance 55% of the total investment.

The most relevant government initiative for research on rare diseases was the creation by ISCIII in 2006, of the Biomedical Research Network on Rare Diseases (CIBERER) in order to act as a research performing body on rare diseases in Spain. CIBERER is a centre orientated towards the development and implementation of cooperative research in the field of rare diseases, performing basic, clinical and epidemiological biomedical research, placing special emphasis on transferring the research from the laboratory to the patient's bedside and scientifically responding to the questions that arise from the interaction between physician and patient. This network acts as a public consortium of 29 institutions; the network has more than 700 professionals integrating 60 research groups and is mainly funded by the Institute of Health Carlos III and is attached to it. The aims of CIBERER are: to improve the resources available for researching rare diseases and rare disease treatments, to promote the integration between basic and clinical biomedical research groups in order to aid collaboration between the laboratory with the clinical setting, to develop cooperative investigational projects that allow for the exploration of new scientific hypotheses and technological developments, to demonstrate

the value of rare disease research, and to establish collaborative efforts with the pharmaceutical and biotechnological industry.

The results of CIBERER's 2011 research activities, organised into seven programmes (Genetic Medicine, Inherited Metabolic Medicine, Mitochondrial Medicine, Paediatric and Developmental Medicine, Neurosensorial Pathology, Endocrine Medicine and Inherited Cancer and Related Syndromes) were made available in 2012 in CIBERER's 2011 Scientific Report. The report describes and updates the activity of each of the research groups that comprise the Centre, including their research lines, training and dissemination activities, scientific publications, ongoing projects, clinical trials and clinical guidelines. In 2011 a reorganisation based on the modifications of the Centre's statutes, greater knowledge of the groups' potentials and the definition of new strategic objectives was undertaken. The structure of Scientific Areas was replaced by the organisation of groups in Research Programmes. The 2011 Action Plan defined certain instrumental measures with a scientific, technical, translational and training slant. A principle network scientific endeavour in 2011 was the start of the Programme for "Genes in undiagnosed Rare Diseases", a major project for applying exome sequencing to many rare diseases in order to discover new genes and variants involved in this kind of pathologies. The report also details actions in the area of translational research, technology transfer, training, outreach, scientific publication, and public awareness.

CIBERER had also defined its strategy for 2012, which was designed to reinforce compliance with the objectives laid down in the Rare Disease Strategy of the Spanish National Health System and follows the main lines drawn and executed through the 2011 plan of action, while taking into account and accommodating budget cuts. The proposed action plan for 2012 emphasises translation and transfer of research and knowledge and includes two new structures: the Platform of Bioinformatics for Rare Diseases (BIER), whose main mission is to cooperate with the experimental groups working with genomic data for its analysis and interpretation; and the Neurogenetics platform, which will provide service performing genetic analysis of rare inherited neuropathies. Another novelty featured in the CIBERER 2012 Action Plan is the call for Cooperative and Complementary Intramural Actions (ACCI), intended to foster cooperative research with an internal but competitive call for which transfer and translational components will be criteria for the funds assignment.

The following institutions give support for academic / industrial research on rare diseases:

- Fund for Health Research (FIS) (which belongs to the Institute of Health Carlos III) funds single and multi-centre research projects as well as technology assessment projects since 2001. Thus, for example 12 Cooperative Health Thematic Health Networks (RETICS) were created, which involved research groups and centres belonging to the National Health System with a budget amounting to €20 million for three years. Two different calls for proposals of projects addressed to study the potential of new orphan medicinal products have been funded by the Ministry of Health, Social Policies and Equality) and managed by the FIS (ISCIII).
- CIBERER (part of the Institute of Health Carlos III) was given funding by ISCIII amounting to €6.2 million in 2007, €8 million in 2008, €7.7 million in 2009, €5.8 million in 2010 and €5.5 million in 2011 for research activities and €5.1 million in 2012 (basic, clinical, epidemiological and translational) in the field of rare diseases.
- *Instituto de Investigación de Enfermedades Raras* – IIER (Institute of Rare Disease Research), within the Institute of Health Carlos III (ISCIII) was founded in November 2003 to promote basic, clinical and epidemiological research on rare diseases to be useful at the NHS structure and currently genetic, molecular biologist and screening methods for discovery new treatments.
- *Federación Española de Enfermedades Raras* – FEDER (Spanish Federation of Rare Diseases) is a federation which includes most Spanish patient organisations for rare diseases. FEDER also provides funding for research on rare genetic diseases in the scope of the national R&D plan.

Since the Rare Diseases Strategy of the Spanish National Health System began, rare diseases have been considered as a priority research area of the Fund for Health Research (FIS) and the Strategic Action in Health (AES) for 2008-2009. Rare diseases are also taken into account in the area of "additional performances" contemplating the strengthening of both basic research and clinical trials or the development of orphan medicinal products.

In 2009 a €12 million budget in R&D&I and more than 700 researchers were made available by ISCIII as resources for translational research into rare diseases.

In late 2009, the Sant Joan de Déu hospital and the Hospital Clinic (both of Barcelona) became the first in Europe to establish a biobank specifically for paediatric tissue. The entity seeks to promote the donation of much needed paediatric tissue, such as tendons, bones, skin, cornea, and heart and lung valves. While organ donations for transplant in the paediatric population are more frequent, tissue donations are lacking. Such

tissues can be vital to rare disease patients. Working with the Transplant Service Foundation³⁹⁰, the new bank will network with other banks and institutions in Spain and other parts of Europe

In 2010 *La Marató de TV3* raised almost €9 million in donations destined to fund biomedical rare disease research projects which are underway at the present time. One of them is coordinated by Hospital Clínic (Barcelona), and is aiming to create a Catalan network for diagnosis and clinical management of haemoglobinopathies (sickle cell anaemia) and other rare anaemias.

In 2011 the GentxGent Foundation (Comunitat Valenciana) received €175'000 Euros from voluntary donors to fund rare diseases research projects.

ISCIII recently created RetBioH (a network of biobank including biobanks for rare diseases) and attached to it with a sustainable funding of €6 million per year, that will be the Spanish leg of BBMRI (the European biobanking infrastructure in process of constitution as an ERIC).

In 2011 the ISCIII launched a call of Collaborative Research Projects with an overall funding up to €10 million for 5 consecutive years aligned with the IRDiRC scientific objectives, funding level, policies and governance structure. Three proposals have been selected for funding at national level: TREAT-CMT, DRUGS4RARE and a collaborative research joint project to create a National Registry for rare diseases at the IIER.

CIBERER and the National Center for Genome Analysis are collaborating in the massive sequencing and analysis of 116 exomes corresponding to 24 rare diseases and/or groups of pathologies, including mitochondrial, hereditary metabolic, neuromuscular, and sensorineural hearing loss disorders, in a bid to uncover the genetic cause of the conditions. Identification of the genetic basis for these diseases could open new diagnostic pathways. It is anticipated that the study will lead to the identification of the genetic defect in at least 50% of the cases studied.

Participation in European research projects

Spanish teams participate, or have participated, in European rare disease research projects including: ANTEPRION, ALS-degeneration, AIP-GENE, ANTIMAL, BNE, CLINIGENE, CHD-PLATFORM, COQ-iPSC, CONTICANGET, CAV-4-MPS, CureFXS, EFACTS, EMSA-SG EUGINDAT, EuroRETT, ENS@T, ENRAH, EUROSARC, EUGINDAT, EUMITOCOMBAT, EUROBOONET, EUROAGENTEST 2, EUROPEAN LEUKEMIA NET, EURENOMICS, EUROSARC, EVI-GENOET, EUROSCA, EPINOSTICS, EUROBFNS, EuroGeBeta, GRIP, GEN2PHEN, GAPVAC, GENESKIN, HSCR, HEART-DM, HMA-IRON, HEMO-IPS, IMMOMECE, INTREALL, INNOVALIV, LEISHMED, LEISHDRUG, LEUKOTREAT, MABSOT, MALARIA AGE EXPOSURE, MCSCS, MEFOPA, MLC-TEAM, MOLDIAG-PACA, NANOTRYP, NEUROKCNQPATHIES, NIMBL, MLC-TEAM, OPTATIO, PNSEURONET, RISCA, RAPSODI, RAREBESTPRACTICES, RD-CONNECT, RD PLATFORM, RevertantEB, SIOPEN-R-NET, SERO-TB, TAMAHUD, TREAT-NMD, TRYPOBASE, WHIMPath.

E-Rare

Spain, represented by the Institute of Health Carlos III (ISCIII), is a partner of the E-Rare. Spain has participated in the two calls for proposals managed by the Fund for Health Research (FIS), the Public Health Agency for Health Research, which is part of the ISCIII. Spain participated in the 2007 and 2009 E-Rare transnational calls with a total of €3.25 million of initial funding committed to the project Spain. Spanish teams participate in 6 of the 13 funded projects/consortia selected following the 1st Joint Transnational Call, and in 6 of the 16 consortia/projects selected for funding in the 2nd Joint Transnational Call, with a total funding of around 580,000€. Spain participated in the 3rd Joint Transnational Call in 2011 and supports a Spanish team in one of the selected consortia. Spain participated in the 4th Joint Transnational Call in 2012: 3 teams from Spain participated in the Consortia funded through the call.

IRDiRC

The Carlos III Health Institute is a committed member of the IRDiRC and will be the funding agency for collaborative research projects awarded by IRDiRC to institutions with the facilities to carry out the project and legal and fiscal address placed in Spain. In 2011 the ISCIII launched a call of Collaborative Research Projects with an overall funding up to €10 million for 5 consecutive years aligned with the IRDiRC scientific objectives, funding level, policies and governance structure. Three proposals have been selected for funding at national level: TREAT-CMT, DRUGS4RARE and a collaborative research joint project to create a National Registry for rare diseases at the IIER. These three projects are national projects, evaluated by an international review panel, but

³⁹⁰ http://www.tsf.cat/eng/quienes_somos/hservicio.php

within the scope of IRDiRC, and targeting IRDiRC objectives, and so communicated to and recognised by its secretariat.

Orphan medicinal products

The Spanish Agency of Medicines and Medical Devices (AEMPS) is the National Authority responsible for evaluating medicines before approval as well as for conducting a continuous supervision post authorisation of its benefits and risks in order to update the approved conditions of use of any medicine. In the case of orphan medicinal products designated at the European level, this evaluation process is undertaken by all national European agencies under coordination of the EMA, i.e. 'centralised procedure'.

Orphan medicinal product committee

No specific activity reported.

Orphan medicinal product incentives

There are specific scientific advice procedures in place at the AEMPS to give guidance and advice to any potential orphan medicinal product development. These procedures can be applied within the context of a centralised advice coordinated by the EMA or on a purely national basis.

Since 2007, there is an annual call for public financing of clinical trials of medicines with no commercial interest. In this call, medicines for rare diseases (either designated as orphan medicines or not) are one of the priorities, together with paediatrics, antibiotics and studies of major interest for the National Health System). In the scope of this call, proposals for studies concerning medicines for the treatment of rare diseases have an outstanding rate of success in obtaining full public financing.

In Spain, the 29/2006 Act on "Guarantees and Rational Use of Medicines and Medical Devices" states in Article 2, referring to supplying and dispensation guarantees of orphan medicinal products, that: "the Government, in order to ensure the supplying of medicines, will be able to adopt special actions in relation with their manufacture, importation, distribution and dispensation. In the case of "orphan medicinal products," (pursuant to the Regulation (EC) number 141/2000 "medicines without any commercial interest") the Government could adopt, besides the above mentioned, other actions related to the economic and fiscal policy of the so-called medicines".

Since June 2010, orphan medicinal product manufacturers have a reduced rebate of 4% (instead of 5%, and 7.5% in the case of products directly distributed to hospitals) on the VAT-exclusive public price of medicines financed by the National Health System if they are not included in the reference price system (Royal Decree 8/2010)³⁹¹.

Orphan medicinal product market availability situation

Access to orphan medicines is extensive in Spain, with all designated orphan medicines authorised at the European level also authorised by the Spanish authorities and included in National Health System coverage.

Almost all authorised orphan medicines are marketed in Spain (47 out of 64, representing 73%, of the drugs with European Market Authorisation). In 2011, 6 new orphan medicinal products were marketed in Spain, being Vpriv (velaglucerase), Siklos (hydroxycarbamide), Cayston (aztreonam), Peyona (caffeine citrate) and Revatio (sildenafil).

Orphan medicinal product pricing policy

Pricing of medicines and access to reimbursement are combined and managed by the Health Ministry's General Subdirectorate of Quality of Medicines and Health Products, part of the Directorate General of National Health Service and Pharmacy. This is common procedure for all prescription medicines. Actual hospital purchase prices are determined by the government of each autonomous community or negotiated individually between manufacturers and each hospital/group of hospitals³⁹².

Orphan medicinal product reimbursement policy

In Spain, when marketing authorisation is granted either by the EMA or AEMPS, the Ministry of Health, Social Services and Equality initiates a procedure to decide on reimbursement of this new product on the national reimbursement list. If a reimbursement status is approved, the pricing is decided simultaneously. Up till now all orphan medicinal products approved by the EMA are reimbursed in Spain in one of these categories: 1) for use

³⁹¹ Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) pp 85-86

³⁹² Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p 85

only in hospitals (hospital Use: H) or 2) in a non-hospital environment, but prescribed only by a specialist doctor (hospital diagnostic: DH).

Currently, 57 orphan medicinal products are fully reimbursed by the National Health System. Nevertheless, in some Regional Governments, there are protocols and systems to follow the access of patients to the treatment under the National Health System coverage.

In 2011, 6 new orphan medicinal products were included in the national reimbursement list. Moreover, a new law which improves the regulation of compassionate use (particularly for orphan medicinal products) and foreign medications legally distributed in other countries but not authorised in Spain came into force in 2009.

Other initiatives to improve access to orphan medicinal products³⁹³

An authorisation procedure for access to non-authorized medicines is in place. The AEMPS authorises either individual access for specific patients (compassionate use) or access to groups of patients through a certain protocol (temporary authorisation of use). The procedure for granting this access has recently been improved (Royal Decree 1015/2009) in order to make it faster, through entirely telematic communication with the hospitals at the same time that it has been reinforced the follow up of safety information by the AEMPS and the information systems.

Compassionate use is available for medicines under investigation for patients with a chronic or life-threatening disease that are not able to be treated satisfactorily with an authorised medicine (based on Regulation (EC) No 726/2004). In the case of authorisation for individualised access, the treating hospital needs to submit a separate application for an individual patient to the Spanish Medicines Agency accompanied by a dossier.

Temporary Use Authorisation is possible for medicines under investigation. The Spanish Medicines Agency is able to set up such an authorisation for medicines under investigation independent of a clinical trial in an advanced phase of clinical investigation as long as the use is for a significant group of patients. The Temporary Use Authorisation will include all the conditions and requirements for use.

Off-label use is based on Act 29/2006 for Guarantees and the Rational Use of Medicines and Healthcare Products, Art. 24. Off label use must be exceptional and limited to those situations with a lack of therapeutic alternatives for a patient. The physician must justify the need for the use of the orphan medicines and inform the patient about potential risks and benefits and obtain his/her written consent.

Medicines not authorised in Spain but in other countries (Royal Decree 1015/2009 of 19 June 2009 for the availability of medicines in special situations) can be authorised exceptionally by the Spanish Medicines Agency when no medicine is authorised (or authorised and not marketed) with the same composition or the available dosage does not allow an appropriate treatment, or when there is no authorised medicine that represents an adequate alternative for that patient available in Spain. Any application needs to be accompanied by the prescriber's clinical report that justifies the clinical need for treatment and the estimated treatment duration, the number of packages required, scientific documentation for using, patient's written consent and the sponsor's conformity, if necessary. The Spanish Medicines Agency will make protocols for using medicines not authorised in Spain when there is a need concerning a significant subpopulation of patients.

The payer for all three described situations is the National Health Service, but in some case the companies act as "sponsors".

Other therapies for rare diseases

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

Respite care is provided for rare disease patients considered as living in a situation of dependency. These services can take the form of nursing homes, day care centres, home care, remote assistance, or as a residential stay such as those offered for free at the Burgos' National Reference Centre for Rare Diseases. These services are either public or private and co-payment is often required. Patients suffering from a disability

³⁹³ Information from the EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner (2011), pp58-59

are eligible for government allowances for resort and spa stays with 20% to 50% of the total cost covered (this includes travel and stay as well as insurance costs).

1.26. SWEDEN

Definition of a rare disease

The Swedish definition of a rare disease is a disorder resulting in an extensive disability with a prevalence of no more than 1 in 10 000 inhabitants. The Swedish Medical Products Agency applies the European Regulation on Orphan Medicinal Products definition, a prevalence of no more than 5 in 10 000.

National plan for rare diseases and related actions

In June 2010, the National Board of Health and Welfare presented a report concerning the organisation of national resources for rare diseases to the Ministry of Health and Social Affairs.

In June 2010, the Swedish Government decided to establish a national focal point for coordination in the field of rare diseases³⁹⁴, a €300,000 project, with the main objective of coordinating rare disease efforts and disseminating knowledge and information within and between health services, NGOs and other stakeholders. The decision represented an important step towards a better use of the resources available for patients with rare diseases and the patients' relatives. On 24 July 2010, the National Board of Health and Welfare was commissioned by the Swedish Government to establish this national focal point in the field of rare diseases.

In November 2010, the Swedish National Conference on Rare Diseases³⁹⁵ was held in Stockholm, to discuss a future national plan or strategy for rare diseases under the EUROPLAN project. The conference allowed stakeholders to meet to discuss a range of policy topics and helped put rare diseases on the national agenda, stimulating discussion concerning a national plan for rare diseases.

At the end of 2011 National Board of Health and Welfare announced the new *National Function* for Rare Diseases (NFSD - *Nationella Funktionen för Sällsynta Diagnoser*). Their work will include the promoting of coherence and coordination of health care resources for people with rare diseases and to accomplish increased coordination with the social insurance, employment services, social services, NGOs and other actors. They will also contribute to the dissemination of knowledge and information and to the exchange of good practice and experiences. NFSD started on 1 January 2012 and the assignment has been entrusted to the non-profit rare disease care facility Ågrenska. An inventory of available resources for people with rare diseases is one of the first tasks for the NFSD.

The Swedish Government decided in October 2011 to assign the National Board of Health and Welfare the task of developing a national strategy for rare diseases. The National Board of Health and Welfare have worked together with the NFSD and other stakeholders to develop the strategy. In November 2012, the Swedish national strategy for rare diseases was transmitted to the government. For the moment the financial implications have not been considered.

On 26 November 2012, a Europlan national conference was held in Stockholm bringing together 140 stakeholders, to follow the elaboration of the national plan for rare diseases. The conference was organised by the Rare Diseases Sweden and focused on how to transform the strategy proposed by the National Board of Health and Welfare into a concrete plan of action to improve care for rare diseases. Health care providers, policy makers and user representatives from across the country signed up to take part in the discussion about how to put the strategy into action.

Centres of expertise

Sweden's health care system is decentralised and run by 21 county councils/regions. In accordance with a 1990 agreement with the Federation of County Councils, the National Board of Health and Welfare has issued a catalogue of providers of specialist care, which is intended to provide recommendations on reference points for local administrators. These centres providing expertise are mostly located at university hospitals. The new NFSD will collect information concerning centres of expertise in Sweden. Some university hospitals receive funding to develop regional centres for rare diseases. Criteria for expert centres are under development.

³⁹⁴ <http://www.regeringen.se/sb/d/13214/a/148634>

³⁹⁵ [http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/FINAL%20Report Sweden%20EUROPLAN%20NC%202010.pdf](http://download.EURORDIS.org/europlan/2%20EUROPLAN%20Guidance%20Documents%20for%20the%20National%20Conference/FINAL%20Report%20Sweden%20EUROPLAN%20NC%202010.pdf)

Registries

There is a National Patient Registry funded by the National Board of Health and Welfare, including the International Classification of Diseases, Tenth Revision (ICD 10) based diagnoses for all in-patient and some out-patient visits (including day surgery and specialist psychiatric care) from both private and public health care providers. This registry is mainly used for statistics.

The centres of expertise, run by county councils/regions, have developed local quality registries to allow them to monitor activities and results. Currently there are approximately 20 registries for various rare diseases. During 2012 a working group was established for the purpose of developing national registries for rare diseases which will provide a tool to measure and monitor relevant patient care activities for patients with rare diseases.

At the national level, around 70 National Quality Registries have been established³⁹⁶ and are supported by the Swedish Association of Local Authorities and Regions (SALAR). All National Quality Registries contain individual-based data concerning diagnosis, treatment interventions and outcomes. These registries are primarily general and do not solely concern rare diseases, although patients with rare diseases may be included, as in, for example, the Swedish Dementia Registry. SALAR encourages managers of registries to apply for funding to become a National Quality Register in order to increase quality of health care on a national level as well as the accessibility of the registry.

The Swedish Association of the Pharmaceutical Industry runs a pilot project that aims to improve the documentation of orphan medicinal products in clinical use through quality registries. At the moment, this project covers Chronic Myelogenous Leukemia, Idiopathic Thrombocytopenic Purpura and Pulmonary Arterial Hypertension.

Sweden contributes to the EUROCARE CF, EUROCAT, SCNIR, and AIR European registries.

Neonatal screening policy

For many years, a newborn screening programme has been in place for phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency and galactosemia in Sweden. However, since November 2010, the programme has been extended to twenty-four disorders. The required blood sample volume remains the same. The additional disorders screened are MCAD deficiency, LCHAD deficiency and other defects in TFP, VLCAD deficiency, dysfunction of the carnitine cycle molecules CPTI, CPTII and CACT, primary carnitine deficiency CUD, Isovaleric aciduria, methylmalonic aciduria MMA, glutaraciduria type I and 2, beta-ketothiolase deficiency, citrullinemia, argininosuccinate lyase deficiency (ASA), arginase deficiency, maple syrup urine disease (MSUD), tyrosinemia type 1, propionic acidemia and homocystinuria.

Genetic testing

Genetic testing is mainly performed by the six clinical genetics units at the University Hospitals of Lund, Gothenburg, Linköping, Uppsala, Stockholm and Umeå³⁹⁷. Some molecular testing, mainly SNP-analysis for single polymorphisms, is done in medical biochemistry units or pathology units without special competence in clinical genetics. There are neither national reference laboratories nor any formal agreements between laboratories regarding co-operation and specialisation. There are no specific national guidelines for genetic testing issued by health authorities.

Genetic tests are reimbursed in the same way as all other medical tests. Laboratories must be authorised by the county councils in order to receive reimbursement (this applies for any laboratory service). There is no private sector of any significance. Genetic testing abroad is possible and is widely used, and there are not any specific regulations opposing this.

Diagnostic tests are registered as available in Sweden for 119 genes and an estimated 175 diseases in the Orphanet database³⁹⁸.

National alliances of patient organisations and patient representation

The Swedish national patient organisation for rare diseases (*Riksförbundet Sällsynta diagnoser*) is a national alliance for rare disease patient organisations. The alliance aims to create a holistic view of the common problems associated with rare diagnoses to support small handicap groups, to ease the particular difficulties of patients with rare diagnoses and to promote and protect human rights. *Riksförbundet Sällsynta Diagnoser* also provides funds to support the empowerment of patient organisations.

³⁹⁶ <http://www.kvalitetsregister.se/>

³⁹⁷ <http://sfmg.se/sv/externalankar>

³⁹⁸ <http://www.orpha.net> Information extracted from the Orphanet database (December 2012).

Patient organisations for rare diseases are mainly sponsored by private sponsors, but they may also receive public sponsorship for specific projects. Although the Swedish healthcare system emphasises both decentralisation and organisation at municipal, county and regional levels, new bills have been passed by the Parliament to support patient organisations and their activities. One bill supported a conference in November 2009 for members and non-members of *Riksförbundet Sällsynta Diagnoser*. Another bill supports further development of a communication platform on the website www.sallsyntadiagnoser.se where a diagnosis database for members will be available. This communication platform will also allow those concerned to reach both formal and non-formal contacts and get in contact directly via a web community and a web forum.

At present, there is no specific platform for the representation of or consultation with patient organisations in policy issues for rare diseases in Sweden.

Sources of information on rare diseases and national help lines

Orphanet activities

Since 2006 the Karolinska Institute has hosted an Orphanet team in Sweden. During 2012 the Orphanet team was integrated with the Regional Centre of Rare Diseases, Karolinska University Hospital. The team collects data on services in Sweden related to rare diseases (for example, specialised clinics, medical laboratories with lists of diagnostics tests, ongoing research, registries, clinical trials, networks, technological platforms, patient organisations and emergency guidelines) for entry into the Orphanet international database. Since 2011, the team provides national information on the Orphanet Sweden website³⁹⁹, offering a national entry point to the Orphanet database in Swedish, giving medical professionals, patients, researchers and other interested parties free access to an encyclopedia and inventory of more than 3000 rare diseases, disease related gene description, orphan medical products and specialised services in Sweden and in 35 other countries. All data are reviewed by experts and abstracts are available in five languages. Orphanet Sweden started a close cooperation during 2012 with the recently installed National Function Point for Rare Diseases and the Information Centre of Rare Diseases to optimise the national information resources. In 2011 and 2012 Orphanet arranged conferences related to the Rare Diseases Day.

A nationwide survey was carried out at the end of 2010 to investigate the primary care of patients with rare diseases. The survey was based on the results of previous rare disease patient surveys and included questions concerning the types of rare diseases encountered by doctors, the diagnostic tools currently in use, what problems doctors face in the care of rare disease patients and how these can be solved. A second aim of the survey was to inform doctors about existing diagnostic tools and Orphanet services. The results demonstrate the importance and need of improving the education of rare diseases for GPs as well as informing professionals about existing web portals for rare diseases, such as Orphanet.

Official Information Centre for Rare Diseases

Since 1999, the Swedish Rare Disease Database has been run by the Swedish Information Centre for Rare Diseases (*Informationscentrum för ovanliga diagnoser*) at the Sahlgrenska Academy of the University of Gothenburg. The Centre is financed by the National Board of Health and Welfare and is a national resource for patients, families and professionals. Apart from producing and maintaining the Rare Disease Database, the Centre offers assistance in information retrieval and works to increase awareness and knowledge about rare diseases. The Centre acts as a clearing house for all information related to rare diseases and for relevant national resources.

The Rare Disease Database of the National Board of Health and Welfare currently includes detailed and expert-validated information about 300 rare diseases. This material is freely accessible at the website of the National Board of Health and Welfare: www.socialstyrelsen.se/ovanligadiagnoser. Each text in the database includes information on symptoms, occurrence, causes, genetics, diagnostics, treatment, national and regional resources, patient associations, courses for patients and for healthcare professionals, national medical specialists, national (and sometimes international) medical centres, social support, other sources of information, and research references.

The material can be printed out easily. There are also concise information sheets for every disease. All the texts in the database are updated on a regular basis. The material is being translated into English and currently more than 160 information texts can be accessed at www.socialstyrelsen.se/en/rarediseases. The database has more than 1 million visitors per year.

³⁹⁹ <http://www.orphanet.se/national/SE-SV/index/hemsida/>

Help line

The Swedish Information Centre for Rare Diseases also serves as a public helpline by answering questions, mediating contacts and giving advice on where to find further assistance. Orphanet Sweden also provides information about national and international rare diseases resources.

Other sources of information on rare diseases

Ågrenska contributes to the dissemination of information by providing information with a holistic perspective, including information on available social services. They also participate in maintaining the Nordic web resource www.rarelink.org and the Ågrenska Academy was established in 2009 and provides streaming live cast lectures and conferences. Experiences and lectures are documented and distributed on Ågrenska's website (about 150 documents).

There is a close cooperation between Ågrenska and the Swedish National Organisation for Rare Diseases.

Updated information on orphan medicinal products has been published by *Läkemedelsindustriföreningen* (LIF)⁴⁰⁰, the trade association for research-based pharmaceutical industry in Sweden.

Riksförbundet Sällsynta Diagnoser has an online database with information on 60 rare diseases.

Good practice guidelines

Professional networks between the University Hospitals of Sweden and within Medical Associations initiates and continuously develops best practices and guidelines for rare diseases. The Best practice clinical guidelines have been elaborated upon as a result of initiatives by Ågrenska and professional networks.

Training and education initiatives

A number of courses are held on the initiative of patient organisations and knowledge centres for rare diseases.

Ågrenska offers families, adults and children the possibility to benefit from educational activities adapted to their needs. They also provide guidance regarding the availability of social services. In 2012 Ågrenska arranged twenty-five national family stays such as empowerment programmes, including two educational days for professionals and six empowerment programmes for adults (adult stays) with a rare disease.

The University hospital teams that provide care for certain rare diseases educate and inform patients and families during educational days about their specific diagnosis. Medical professionals and representatives from the social services are given specialist training. The Orphanet team also helps specialists in training about how to find validated information on rare diseases.

National rare disease events in 2012

Rare Diseases Sweden organised a number of events to mark Rare Disease Day. The campaign kicked off in the months prior to the Day and included a photography exhibition and a lecture tour over the winter of 2011-2012 to establish contact between the Swedish Alliance of Rare Diseases and hospitals working with rare disease patients.

On 29 February 2012, volunteers organised an event at the Central station of Stockholm to reach the general public and raise awareness. On the same day, a number of meetings and think tanks were held: a range of stakeholders were invited to discuss the content of the national plan/strategy of rare diseases.

A rare disease scholarship was bestowed to a young volunteer in a rare disease patient organisation to mark the day. In addition a flash mob was organised to mark the Day.

On 22 February a regional meeting to celebrate the Day organised by Orphanet in Stockholm together with the Swedish Alliance of Rare Diseases under the auspices of the Karolinska University Hospital and the Karolinska Institutet. The theme of the meeting was "Shaping regional centres for rare diseases" and was attended by about hundred representatives of health care professionals, researchers, patients, pharma industry, health authorities and politicians. The regional meeting was one of a series of Regional meetings across Sweden to mark Rare Disease Day

On 26 November 2012, a Europlan conference was held in Stockholm, to follow the elaboration of the national plan for rare diseases.

Rare Diseases Sweden held their annual meeting on 24-25 November 2012, welcoming 50 participants.

⁴⁰⁰ <http://www.lif.se/>

Hosted rare diseases events in 2012

No specific reported activity.

Hosted Nordic Events

The Nordic Council has funded a project that investigated possible areas for Nordic networking and cross-country cooperation in the field of rare diseases. One of these projects is arranging Nordic conferences.

Research activities and E-Rare partnership

National research activities

The Swedish Research Council (SRC) is a government agency under the Ministry of Education and Science. The agency evaluates and prioritises research in medicine, pharmacy, odontology and dental care sciences and decides on project grants in these fields. Project funding is based on quality criteria (bottom-up procedure) and not subject to prioritisation based on research area, with a few exceptions. SRC also makes decisions to provide financing for principal investigators in areas of research where directed support is of strategic value.⁴⁰¹ Rare diseases are thus funded through a yearly call for proposals for project grants; however, there is no dedicated budget for rare diseases. Instead, applications dealing with rare diseases compete with other applications on the basis of the quality of the proposal and not subject to prioritisation of research areas, with a few exceptions. Approximately 80 research projects on rare diseases were funded by SRC.

Medical research on rare diseases is also supported by a number of private foundations. However, these grants are not specifically dedicated to rare diseases.

Research on rare diseases is performed at many universities and university hospitals. This research is supported by grants from the government as well as from non-governmental foundations. Clinical research concerning rare diseases is partly supported by county councils/regions and clinical trials are partly sponsored by orphan drug companies. Some 50 national hospital units and 30 university departments involved in research activities are registered in the Orphanet database.

The Swedish Cancer Society and the Childhood Cancer Foundation are examples of a non-profit organisation which contributes to the funding of cancer research (including rare cancer), information-sharing and supporting activities which aim to improve cancer treatment and care. Research projects are funded following the same policy as that of the SRC.

It is impossible to separate support for rare disease research from support for orphan medicinal product development, as these research efforts are often mixed. In all likelihood, however, probably very little money directly supports orphan drug development.

An example of a centre performing research on rare disorders is Mun-H-Centre. Their activities focus on oral health and orofacial functions such as eating, speech, facial expression and saliva control in rare diseases. Since 1996, data on oral health and orofacial function have been collected through structured parental and clinical observations and registered in a database. Selected data from the database is presented at the Mun-H-Centre website⁴⁰² and the information is updated regularly.

The Family programme and Respite service at *Ågrenska* provides the opportunity to meet a large number of children with rare diseases. During family stays using an assessment form (validated by University of Gothenburg, Institute of Psychology), *Ågrenska* performs systematic observations of the children in their school, pre-school and leisure activities, and the results are put together in a database.

National participation in European research projects

Swedish teams participate or have participated in the following European research projects for rare diseases: AIPGENE, ACADEMIC GMP, ANTEPRION, BIOMALPAR, BNE, CHD PLATFORM, CUREHLH, CLINIGENE, DRUGSFORD, DSDLIFE, EMVDA, EUMITOCOMBAT, ENCCA, EURAPS, EUCLYD, EURODS, EUROBONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EVI-GENORET, EMSA-SG, EUROCRAN, EURADRENAL, EURAMY, EURO-GENE-SCAN, GENESKIN, FNAIT, HDLMOICS, IMPACTT, INTREALL, INNOVALIV, INHERITANCE, NMD-CHIP, LYMPHANGIOGENOMICS, MANASP, MOLDIAG-PACA, NEUPROCF, NEOTIM NEUROPRION, NEWTBDRUGS, PRIBOMAL, PWS, TRYPOBASE, TB-DRUG OLIGOCOLOR, TREAT-NMD, RD PLATFORM, RDCONNECT, RAREBESTPRACTICES, and VITAL.

⁴⁰¹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp20-21).

⁴⁰² www.mun-h-center.se

E-Rare

Sweden is not currently a partner of the E-Rare project.

IRDiRC

Swedish funding agencies have not yet committed funding to the IRDiRC. However, the progress of the consortium activity programme is followed by Orphanet Sweden and the National Board of Health and Welfare.

Orphan medicinal products

Orphan medicinal product committee

A few Orphan medical product expert committees in Sweden have been formed on the initiative of the Swedish Society of Medicine and of local county councils, respectively.

Orphan medicinal products incentives

The Medical Products Agency (MPA)⁴⁰³ is responsible for the regulation and surveillance of the development, manufacturing and marketing of medicinal products in Sweden. Regarding orphan medicinal products, centralised marketing authorization application to the European Medicines Agency (EMA) is mandatory. The applications are assessed by the Committee for Human Medicinal Products (CHMP) at the EMA and the decision, valid for the whole of the EU, is granted by the Commission.

The MPA can waive the fees for clinical trial applications and provide scientific advice for researchers, applicants and companies lacking support from the pharmaceutical industry. Concerning the provision of free of charge IMP by clinical trial sponsors, Swedish law allows exemptions: should an obligation to perform a trial after marketing have been a condition of the marketing authorisation being granted for an orphan drug. The same could apply for all clinical trials and IMPs, not just orphan drugs on the condition that the clinical trial is performed without the participation of the pharmaceutical industry or that the clinical trial is special importance to public health.

Orphan medicinal product market availability situation

According to the MPA, out of the 78 orphan medical products (OMPs) authorised by December 2012 The Dental and Pharmaceutical Benefits Agency had decided to reimburse the following 38 OMPs (some with restrictions): Fabrazyme**, Replagal**, Glivec** (for CML), *(withdrawn from registry of OMPs for remaining orphan designated conditions), Tracleer**, Somavert, Zavesca (for Niemann-Pick's disease), Carbaglu, Aldurazyme, Ventavis, Onsenal (withdrawn register medicinal products human use), Wilzin, Xagrid, Orfadin, Prialt, Revatio, Nexavar, Sutent*, Thelin (withdrawn register medicinal products human use), Exjade, Sprycel, Diacomit, Inovelon, Cystadane, Revlimid, Increlex, Tasigna, Thalidomide Celgene, Volibris, Firazyr, Ceplene, Mepact, Afinitor*, Cayston, Nplate, Revolade*, Esbriet, TOBI Podhaler, Votubia. The DPBB decided not to reimburse the following 21 OMPs: Busilvex, Litak, Lysodren, Pedeia, Xyrem*, Naglazyme, Myozyme, Evoltra, Savene, Elaprase, Soliris, Atriance, Glilolan, Yondelis, Torisel, Kuvan, Vidaza, Mozobil, Ilaris*, Arzerra, VPRIV⁴⁰⁴. Of note, Zavesca** for treatment of Gaucher's disease has been removed from the list of reimbursed OMPs by the DPBB. Reimbursement information is lacking for a number of OMPs, some of which have been withdrawn from the market but the majority being products authorised late in 2011 and 2012. Several OMPs are marketed in Sweden without general reimbursement.

Orphan medicinal product pricing policy

The Dental and Pharmaceutical Benefits Agency whether a new medicinal product should be reimbursed for community use and approves its pharmacy purchase and selling price. Manufacturers of hospital-use drugs can negotiate directly with the county councils⁴⁰⁵.

Orphan medicinal product reimbursement policy

Reimbursement decisions are made by The Dental and Pharmaceutical Benefits Agency⁴⁰⁶, a government agency commissioned to make decisions on state subsidies for dental and pharmaceutical products. If a positive decision on reimbursement has been made by the agency, OMPs are fully reimbursed by social

⁴⁰³ www.mpa.se

⁴⁰⁴ *The product has been withdrawn by the sponsor from the Registry of Orphan Medical Products, **The product has been removed from the Registry of Orphan Medicinal Products since its 10 years of market exclusivity has expired. For Glivec the applies to the acute lymphatic leukaemia indication only.

⁴⁰⁵ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011) p117

⁴⁰⁶ www.tlv.se

insurance in Sweden (there are no conditions specific to orphan drugs) and are available through hospital and community pharmacies when prescribed by a specialist physician or a general practitioner.

Other initiatives to improve access to orphan medicinal products

Compassionate use of OMPs/non-OMPs has been introduced in Sweden under the responsibility of the MPA. For OMPs not yet available in Sweden, the MPA can approve “named patient prescription” of a certain drug for a certain patient on a yearly basis: this procedure also applies for non-OMPs.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Ågrenska offers families, adults and children the possibility to benefit from programmes that provide guidance to patients regarding latest medical knowledge, available social services as well as educational and holistic activities adapted to their needs.

The Mo Gård Group coordinates measures for patients with communication disabilities, some of which are linked to rare diseases.

The Swedish Act concerning Support and Service for Persons with Certain Functional Impairments (*Lagen om stöd och service till vissa funktionshindrade - LSS*) is an entitlement law that ensures good living conditions for people with extensive and permanent functional impairment, ensuring that they receive the help they need in daily life and that they can influence the support and services they receive. This law is most relevant for rare diseases because in most cases, rare diseases entail functional impairment. Accordingly, municipality institutions provide fully reimbursed activities, such as respite care services, therapeutic recreational programmes and services aimed to promote the quality of life.⁴⁰⁷

1.27. UNITED KINGDOM

Definition of a rare disease

There is no official definition of a rare disease in the UK. The National Specialised Commissioning Team (NSCT) commissions services, products or technologies for conditions affecting usually less than 500 patients across England, which currently covers around 60 conditions, diagnoses or procedures (mostly concerning genetic diseases, especially in children). The definition for specialist commissioning is the presence of conditions requiring a planning population of 1 million or more, as explained in the following section. Similar arrangements apply in the devolved administrations of Scotland, Wales and Northern Ireland.

National plan/strategies for rare diseases and related actions

Current organisation of health care for rare diseases in the UK

In the past, the basic concept in the National Health Service is not that of ‘rare diseases’ but rather that of ‘specialised services’. However, this changed as of 1 December 2012, in preparation for the new framework for healthcare delivery in England. Whilst all aspects of specialised service provision remain under the control of the NHS, for the first time, rare diseases policy (including the development of the UK Plan for Rare Diseases) is now the responsibility of the genetics and genomics team in the Health Science and Bioethics Division of the Department of Health England.

The majority of services are commissioned by Primary Care Trusts (PCTs) in partnership with general practice. A large proportion of the money is spent on services for conditions affecting large numbers of people. Services for rarer or more unusual conditions, known as “specialised services” are subject to different commissioning arrangements. Specialised services are those with low patient numbers but which need a critical mass of patients to maintain quality and make treatment centres cost-effective; a catchment population of more than 1 million is needed. As these services are high-cost and low volume, under arrangements which were strengthened by the Carter Review in 2006, PCTs group together to commission such services through 10

⁴⁰⁷ <http://www.vgregion.se/upload/HoH/Kansli/R%c3%a5d%20och%20st%c3%b6d/Iss-engelska-hso-hoh.pdf>

specialised commissioning groups (SCGs). Each SCG covers a population of approximately 3-7 million people. The National Specialised Commissioning Group (NSCG), co-ordinated specialised commissioning.

Since 2010, the Advisory Group on National Specialised Services (AGNSS) has operated as the advisory body for England covering specialised services and treatments for extremely rare conditions typically affecting fewer than 500 patients.

In 2012, proposals were developed to disband the Advisory Group on National Specialised Services (AGNSS). This will take effect as of April 2013. The services currently commissioned on a national basis will continue to be commissioned by a new NHS Commissioning Board. The Clinical Reference Groups during the transition of specialised services to the new NHS Commissioning Board will continue to be the source of clinical advice as the NHS Commissioning Board moves forward in its direct commissioning role. The Clinical Advisory Group (CAG) for Prescribed Services took evidence from these Clinical Reference Groups and has released a report⁴⁰⁸ outlining which services should be directly commissioned by the new NHS Commissioning Board (many of these are services for rare diseases). A public consultation⁴⁰⁹ on specialised services to be commissioned nationally by the NHS Commissioning Board was launched in December 2012, with the results to be published in early 2013.

Different arrangements exist in Scotland, Wales and Northern Ireland. NHS Wales has recently undergone reorganisation and since April 2010, 7 Local Health Boards are responsible for planning health services for their population. For specialised services, the Welsh Health Specialised Services Committee (WHSCSC) is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales. In Scotland, the National Services Division commissions nationally designated specialist services funded by top sliced funding from the Scottish Government Health Directorates: a service may receive designation if the service need is very low and that there is a clinical need for such a service. In Northern Ireland, the Health and Social Care Board along with 5 local commissioning groups commission services.

Funds for care of patients with rare diseases are included in the current expenditure within the general NHS budget, although there is a separate budget for nationally commissioned service. Also each of the 10 specialist commissioning groups in England has its own budget, pooled from constituent PCTs: there are budgets for the equivalent structures in Scotland, Wales and Northern Ireland.

Steps towards a national plan/strategy for rare diseases

The Department of Health launched a consultation on a UK Plan for Rare Diseases on 29 February 2012 (Rare Disease Day). The consultation ran for 12 weeks and showed strong support for a UK Plan for Rare Diseases. Over 350 consultation responses were received from a range of sources including patients, carers, academics, clinicians, researchers and patient support groups. A summary of the consultation responses was published on 16 November 2012⁴¹⁰.

Throughout 2012, healthcare services in England were making preparations in readiness to transfer to a new delivery and governance system. As part of the changes, patient services for those with rare disease continued to be part of specialised services, led by the NHS Commissioning Board. However, for the first time, there is now a nominated lead for rare diseases policy within the Department of Health (DH). The DH rare diseases policy lead will have responsibility to deliver the UK Plan for Rare Diseases in line with EU recommendations.

A new report entitled *Forgotten Conditions: Misdiagnosed and Unsupported, How Patients are Being Let Down*⁴¹¹ issuing from a roundtable of stakeholders from government, academia, and medicine held in June 2012, finds that low prevalence disorders are little understood and frequently misdiagnosed in the United Kingdom. The report also evokes the “postcode lottery” rare disease patients face, in which access to service and treatment depends upon the part of the UK in which one resides, with patients in Wales and Scotland enjoying greater access for certain conditions than those in England. The report offers several recommendations to remedy the current state of affairs, including: developing shared care pathways for best practice clinical guidance and expertise; education for medical students that broadens the scope of rare disease diagnostics; harnessing new technology to improve diagnostics; encouraging and supporting self-diagnosis and self-care for patients; and ensuring that the National Commissioning Board takes rarer conditions into account when developing guidance for Clinical Commissioning Groups.

⁴⁰⁸ <http://www.dh.gov.uk/health/2012/09/cagreport/>

⁴⁰⁹ <http://www.commissioningboard.nhs.uk/ourwork/d-com/spec-serv/consult/>

⁴¹⁰ <http://www.dh.gov.uk/health/2012/11/response-rare-disease/>

⁴¹¹ <http://www.2020health.org/2020health/Publications/publications-2012/forgotten-conditions.html>

Other related actions

On 25 January 2012, the Human Genomics Strategy Group, which was set up in 2010 as part of the Government's response to the House of Lords Science and Technology Select Committee's report on Genomic Medicine with a remit to develop strategic options for genomics in the NHS and to oversee broader developments in relation to genetics in NHS services, produced its report: *Building on our inheritance: genomic technology in healthcare*. This presented a vision for the development and adoption of genomic technology in healthcare and made recommendations on its implementation. The report and its recommendations were welcomed by the UK Government.

Following on from the report, on 10 December 2012 the Prime Minister announced that the UK will sequence 100,000 whole genomes of NHS patients at diagnostic quality over the next three to five years, earmarking £100 million:

- to train a new generation of British genetic scientists to lead on the development of new drugs, treatments and cures, building the UK as the world leader in the field.;
- to pump-prime DNA sequencing for cancer and rare inherited diseases; and,
- to build the NHS data infrastructure to ensure that this new technology leads to better care for patients

The Department of Health has earmarked up to £100 million for the genomics initiative, which will support development of skills and data infrastructure within the NHS and will pump prime the sequencing work. Rare diseases is one of the three priority areas of the initiative, along with cancer and infectious disease.

Centres of expertise

The National Specialised Commissioning Team (NSCT) funds designated centres for the diagnosis and/or care of particular conditions. In line with the remit of the NSCT, designated centres provide services for conditions generally affecting less than 500 and no more than 1000 people nationally. Specialist centres themselves can apply for national commissioning of a particular service, subject to the agreed eligibility criteria.

Genetic services are commissioned regionally by the SCGs. Genetic testing and counselling is thus available regionally and for some conditions in specialist centres, often linked to an area of research. Genetic counselling is an officially recognised profession and training courses are available. These Genetics Centres help direct and sign-post patients and colleagues as regards centres of excellence and specialised services.

The Department of Health issued a report⁴¹² in September 2012 specifying which specialised services for rare diseases should be commissioned at the national level from April 2013. . National commissioning establishes national centres of expertise for a specific disease and streamlines funding to one centralised source rather than being scattered amongst different local budgets.

Arrangements are in place enabling patients in Scotland, Wales and Northern Ireland to access designated centres although funding is provided by the relevant body in each country. Regional specialist services also exist for genetic diseases but these are funded separately. There is an annual call for applications for national commissioning and designation. Research and epidemiology are not funded under this system.

There has been some criticism from patient groups that the lack of a co-ordinated approach to services for rare conditions engenders late, missed or incorrect diagnoses – sometimes with severe health consequences. A range of wait targets and measures are applied across the NHS: the target of particular importance to patients with rare diseases is the 'wait' target (the maximum wait from first contact with a doctor to initiation of definitive treatment). This implies a very strict approach to establishing a definitive diagnosis quickly as this wait is viewed from the patient's perspective.

An article⁴¹³ appearing in the *Orphanet Journal of Rare Diseases* applies the Systematic Component of Variation (SCV) in order to look at access to nationally commissioned services in England, particularly for highly specialised healthcare, generally affecting fewer than 500 people in England or involving services where "*fewer than 500 highly specialised procedures are undertaken each year*". Centralising specialised services in a few centres ensures a volume high enough to maintain excellence, although there is an obligation to ascertain that patients geographically far from such centres are not disadvantaged. The authors applied the Systematic Component of Variation, taking "access" (measured as "service use") in order to study access to services commissioned by the National Specialised Commissioning Team (NPCT) in England. The results of this study suggest that "*...equity of access can usually be achieved at about five years after establishing a service, and this is not dependent, within the geography of England, on the number of centres designated*".

⁴¹² <http://www.dh.gov.uk/health/files/2012/09/Clinical-Advisory-Group-for-Prescribed-Services.pdf>

⁴¹³ <http://www.ojrd.com/content/7/1/85/abstract>

The UK Genetic Testing Network (UKGTN – see page 7 under “Genetic Testing”) has been reviewing genetic testing rates for rare conditions, by geographical regions, based on information from the UKGTN member laboratories. It finds variation in genetic testing rates over the past four years although it is suggested that this is likely due to data quality. This is improving and should yield results for 2011/12 that will be published.

A report⁴¹⁴ of the Joint Committee on Medical Genetics released in 2012 identifies the challenges inherent in integrating genomic medicine into the wide range of existing clinical areas. Amongst the points raised in the report, is the need for genetics sub-specialist training in existing clinical areas such as paediatrics and antenatal care. The report encourages the development of such training to complement and collaborate with existing genetics infrastructures. To combat inequity in the availability of access to specialist centres for heritable disorders, the authors recommend *“the formal inclusion in the new commissioning structures of resourced, multidisciplinary expert groups, which may be specialty or disease specific depending on the context, able to give advice (via Public Health England or otherwise) on specifications for quality assured pathways to assist commissioners”*.

Registries

In the UK registries are kept for individual conditions and some groups of conditions, including congenital anomalies.

In England, a government-backed initiative will allow researchers unprecedented access to anonymised patient health records. The Clinical Practice Research Datalink (CPRD) is a new observational data and interventional research service of the National Health Service (NHS), jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is *“... designed to maximise the way anonymised NHS clinical data can be linked to enable many types of observational research and deliver research outputs that are beneficial to improving and safeguarding public health”*. Data confidentiality is a top priority for the new service and several mechanisms are in place to protect patient privacy. Access to patient data could help rare disease researchers advance knowledge and understanding of rare conditions.

The United Kingdom contributes to the following European registries: EUROCAT, EIMD, TREAT-NMD, AIR, EUROCARE-CF, EURO-WABB, EUHASS, EUROPAC, SCNIR, European Prader-Willi database and EUROWILSON.

Neonatal screening policy⁴¹⁵

Under current policy in the United Kingdom, newborn screening is performed for five disorders using blood spot tests: phenylketonuria, congenital hypothyroidism, sickle-cell disorders (haemoglobinopathies), cystic fibrosis and medium chain acyl CoA dehydrogenase deficiency. There are some variations in the four countries of the UK.

Newborn screening is performed in England for phenylketonuria, congenital hypothyroidism, sickle cell disease, cystic fibrosis and medium-chain acyl-CoA dehydrogenase deficiency. Currently all babies in Scotland are offered screening for phenylketonuria, congenital hypothyroidism, cystic fibrosis, sickle cell disease and medium-chain acyl-CoA dehydrogenase deficiency. In Wales screening is offered for as part of routine care for hypothyroidism, cystic fibrosis, phenylketonuria and Duchenne Muscular Dystrophy (boys only). In Northern Ireland Universal screening of all infants at 5 days of age is offered for phenylketonuria, congenital hypothyroidism and cystic fibrosis; screening for homocystinuria and tyrosinaemia is also offered; and screening for medium chain acyl CoA dehydrogenase deficiency (MCADD) has been available from August 2009 and screening for sickle cell started in April 2010. An official list of screening policies is available <http://www.screening.nhs.uk/policydb.php>.

The National Health Service revised its screening programme standards in 2011 for sickle cell disease and thalassaemia: the revised screening standards provide new material relating to objectives and performance indicators and will take effect from April 2012.

Genetic testing

In the UK, genetic testing for rare inherited conditions for patients being managed by the National Health Service are usually provided by laboratories that are part of a Regional Genetics Centre. Each Regional Genetics Centre comprises a clinical service and laboratories (molecular, cytogenetics and biochemical) that are usually

⁴¹⁴ <http://www.phgfoundation.org/reports/12093/>

⁴¹⁵ <http://www.screening.nhs.uk/programmes>

co-located. There are 23 regional Genetics Centres that are situated in tertiary hospitals. There are also a number of specialised laboratories that provide some genetic testing. For example there is a network of laboratories that provide genetic testing for haemophilia and other individual laboratories testing for specific rare conditions such as retinoblastoma or porphyrias.

Commissioning policy in the UK identifies clinical genetics (clinical service and laboratory provision) as a specialised service. The specialised services are commissioned differently in each country of the UK. As noted above, In England specialised services are commissioned by Specialised Commissioning Groups or by the national commissioning team. In Scotland there is a consortium arrangement, in Wales the Welsh Health Specialised Services Committee is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales, in Northern Ireland the Regional Medical Services Consortium informs the Health and Social Services Boards who commission genetic services.

All the molecular and cytogenetic laboratories across the whole of the UK which are part of a Regional Genetics Centre are members of the UK Genetic Testing Network (UKGTN – www.ukgtn.nhs.uk). The focus for the UKGTN is to support equity of access to genetic testing services for patients being treated by the National Health Service for rare inherited conditions. The Network is a collaborative group of genetic testing laboratories, clinical geneticists, genetics commissioners and patient representatives.

The core functions of the UKGTN include:

- Approval of molecular, cytogenetic and specialist laboratories for membership where quality standards are met;
- Audit/review of testing provision in order to highlight any areas where there may be inequity of access to genetic testing and to review laboratory compliance in meeting national standards;
- Evaluation of new genetic tests for clinical utility and scientific validity to recommend new testing services for NHS funding through a process called the Gene Dossier process;
- Developing mechanisms to improve the commissioning of genetic services such as standard laboratory currencies;
- Maintaining a publicly available free online database of the member laboratories showing where national services are available and the providers of the tests listed in the NHS Directory of Genetic Testing. The database also provides access to approved gene dossiers and testing criteria;
- Advising NHS policy developers, the Department of Health, the National Specialised Commissioning Team and the National Institute for Health and Clinical Excellence (NICE) on new developments and provide a view on policies that impact on the provision of genetic testing services;
- Providing advice to genetics commissioners on new services and funding requirements.

It has long been recognised that the commissioning arrangements across England vary considerably for clinical genetics services and their associated laboratories. The UKGTN Commissioning working group explored the arrangements for the Specialised Commissioning Groups in each region and published a report in March 2011 making recommendations and providing guiding principles. Although commissioning organisations are set to change following the White Paper on Liberating the NHS, the principles developed by the UKGTN can be applied in any setting.

The Government response to the House of Lords inquiry into genomic medicine (the inquiry took place in 2008 and the Government response was published in 2009) states that the Department of Health will “continue, via the UKGTN, to monitor commissioning structures within genetics and genomics and to establish the Human Genomic Strategy Group. The Board and three working groups met during 2010 and 2011 and a report was published in January 2012. The report referenced UKGTN in supporting commissioning, including ongoing collaboration with NICE, genetic test evaluation, monitoring quality of member laboratories and supporting the medical genetics Clinical Reference Group.

The term “reference laboratories” is commonly used but it is often country specific and can also refer to different functions depending on the pathology discipline. In England there are two National Genetics Reference Laboratories based in Wessex and Manchester. These laboratories were funded by the Department of Health from 2002 to 2012 to support the UK genetic laboratory centres by bringing new technologies into service. The specific remit of the laboratories includes: technology development, assessment and validation; developing new quality management systems; developing reference and control reagents; developing information systems for genetics; and providing advice to government and other bodies.

The National Genetics Reference Laboratory in Manchester has developed particular expertise in health informatics and bioinformatics applied to genetic medicine. Its current work programme includes the support and development of databases and software tools used in genetic analyses, bioinformatics training for clinical scientists and developing best practice and support for clinical bioinformatics. It also participates in a

number of UK and EU funded projects addressing health and bioinformatics issues in genetic medicine, including the GEN2PHEN⁴¹⁶ and EUCERD projects on clinical coding. UKGTN has also commissioned NGRL Manchester to develop a clinical genetics data set for use in the NHS and make recommendations to improve the laboratory information systems and their interoperability with NHS systems and other genetic centres.

When laboratories request UKGTN to evaluate a new tests for inclusion on the NHS Directory of Genetic Disorders/Genes for Commissioning an integral component of the Gene Dossier requires the submitting laboratories to develop 'testing criteria' (TC). The TC identifies the key features of the disorder, indicates the types of referrers who would be expected to order the test and aims to ensure that a particular genetic test is being used for the appropriate target population, i.e. those who are most likely to have the condition. TC can also have an educative role and are a helpful guidance tool. If a clinician is required to complete a TC form then they will get a succinct picture of what may well be a disease with which they are not familiar. TC are available from the UKGTN website by searching for testing services using the online database. Between 2004 and 2012 the UKGTN had evaluated 371 gene dossiers and made recommendation for 293 tests to be available for NHS service. During this time 312 testing criteria were developed. There are more testing criteria than Gene Dossiers approved because some TC have been developed for tests already provided by laboratories prior to the introduction of TC. A long term goal for the UKGTN is to draw up TC for all conditions available through the UKGTN including those that pre-date the development of TC in 2006. The Clinical Molecular Genetics Society also develops best practice guidelines which are available from their website. Individually laboratories may develop referral guidelines for local use.

All NHS services are required to return data to commissioners on service activity in order to inform contracts and future developments. Historically genetics laboratories used a system of "workload units" with one unit being equivalent to one minute of working time. There was little standardisation and laboratories applied them inconsistently. Consequently the UKGTN, in collaboration with professional organisations, developed a system that would be easy to use and consistently applied. The system is called Genetic Units (GenUs) and can be applied to laboratories that use both molecular and cytogenetic techniques. It is based on a system of 8 weighted bands. The molecular element is based on amplicons and the cytogenetic element is based on the cytogenetic methodologies but the system shares weightings. One of the major benefits of this robust system is that it can be expanded and adapted to cover technological developments. Additional bands with new weights can be added or a disorder can be moved from one band to another if technology makes testing more efficient and less labour intensive. It has been agreed through the Medical Genetics Clinical Reference Group that the GenU system is adopted for all activity relating to clinical genetics. It will become the standard measurement for all contracted activity related to all service specifications that include molecular pathology activity.

The CMGS issued an annual audit⁴¹⁷ in 2013 of genetic testing activity in 2011-12. Such information is valuable to understanding the rare disease demand for testing and pre- and post-natal activity in this area. The UK audit includes number of samples, number and type of disease, number and type of tests sent for analysis and staff/workload across laboratories.

Nowgen, a leading UK centre for genetics seeking to inform and improve genetic medicine via training, education, public engagement, research and innovation, issued its Review and Programme for 2011-2012⁴¹⁸ in 2011. Nowgen, working with Orphanet UK, will continue its commitment to facilitating access to high quality information on rare diseases and orphan medicinal products for professionals, patients and the public.

There are no restrictions on either clinicians or laboratories sending samples abroad for testing however laboratories receiving samples are normally expected to comply with recognised accreditation standards and take part in external quality assessment.

Diagnostic tests are registered as available in the UK for 644 genes and an estimated 747 diseases in the Orphanet database⁴¹⁹. Between 2004 and September 2012 the UKGTN has recommended tests for 604 disorders and 810 genes for NHS commissioning in addition to 11 panel tests using Next Generation Sequencing (with some of these panels testing over 100 conditions).

National alliances of patient organisations and patient representation

The major alliances representing rare disease patient organisations in the UK are Rare Disease UK, the Specialised Health Care Alliance (SHCA) and the Genetic Alliance UK⁴²⁰ (formerly the Genetic Interest Group).

⁴¹⁶ www.gen2phen.org

⁴¹⁷ http://www.cmgs.org/CMGS%20audit/2012%20audit/CMGSAudit11_12_FINAL.pdf

⁴¹⁸ <http://www.nowgen.org.uk/CubeCore/uploads/documents/NowgenReviewandWorkProgramme20112012.pdf>

⁴¹⁹ Information extracted from the Orphanet database (December 2012).

⁴²⁰ <http://www.geneticalliance.org.uk/>

Rare Disease UK was established in November 2008 as a joint initiative between Genetic Alliance UK and others in response to the unmet health care needs of families who currently struggle to get access to integrated care and support from the NHS.

Rare Disease UK

Rare Disease UK is an alliance of patients, clinicians, industry, academics and researchers campaigning for a strategic plan for rare diseases in the UK. Rare Disease UK⁴²¹ (RDUK) has been lobbying for the “implementation of a strategy for integrated service delivery for rare diseases to ensure quality care and the efficient use of limited NHS resources and scarce expertise” in response to the Council Recommendation. Since its establishment, the RDUK has successfully “developed links with key officials in all four governments and NHS of the UK; [gained the] support of a broad range of stakeholders including over 100 patient organisations, pharmaceutical companies, clinicians, academics and individuals; established five Working Groups comprising experts from a variety of fields to investigate various aspects of a strategy for rare diseases and make recommendations to the government; and provided a single voice to drive forward a strategy for rare diseases”. In November 2008, Rare Disease UK launched in the UK to “campaign for the adoption and implementation of national plans in each of the UK’s home nations” (England, Scotland, Wales and Northern Ireland). This past year, the five Working Groups of Rare Disease UK have been busy developing recommendations for a strategy for rare diseases. A consultation document⁴²² on the initial findings of the Working Groups was released for feedback in October 2010 from all relevant stakeholders located inside or outside of the UK.

Specialised Healthcare Alliance (SHCA)

England’s Specialised Healthcare Alliance (SHCA) was formed in 2003 specifically to lobby for rare disease patients and those with other complex illnesses that need specialised, frequently expensive, medical care. In 2010 the SHCA issued an overview⁴²³ and critique of England’s new arrangements for health service commissioning for small patient populations and has developed recommendations to enhance the approach to cost assessment of treatments for these patients. A discussion of the ethical framework that has been introduced to the assessment process for determining cost effectiveness is provided. The Coalition Government has decided to transfer responsibility for the assessment of ultra-orphan technologies to NICE with effect from April 2013. Meanwhile, partly in response to lobbying by the Alliance, a Specialised Services Commissioning Innovation Fund has been announced to help support the evaluation and adoption of new technologies for smaller patient populations.

In 2011 the SHCA published a new report. “Leaving No One Behind: Delivering High Quality, Efficient Care for People with Rare and Complex Conditions⁴²⁴” which takes stock of recent developments in specialised commissioning and “identifies a series of key drivers in delivering improved care and value for people with rare and complex conditions”. These include building on the Carter Review of Commissioning Arrangements for Specialised Services in 2005/06 (which “...marked a watershed in the development of associated policy and has yielded real benefits for patients in the years that followed); the impetus of the patient organisations as a vehicle to “drive up standards”; improved patient-physician collaborations; the contribution of NICE quality standards; the development of multidisciplinary networks; outcome measures that maximise effectiveness and efficiency; and the development of patient registries with sharply focused datasets.

To produce this report, the SHCA organised a series of nine workshops focussing on quality and productivity in services including rare cancers, haemophilia, blood and marrow transplantation which fed into the report “Leaving No One Behind”

Stemming from the recommendation in this report concerning the central importance of patient registries in specialised care, the SHCA has now produced the *Registries Guide 2011*⁴²⁵. Intended for use by patient organisations - particularly those representing people with rare and complex conditions – the guide seeks to respond to two key questions: would it be useful and practicable for a particular patient organisation to set up a registry and what are the key issues that must be taken into account when setting up a registry. The guide also provides tips, case studies and useful links.

The Alliance arranged further workshops in 2012 looking at some of the key issues raised *Leaving no one behind*, notably around the role which shared decision-making with patients could play in assisting earlier diagnosis of rare conditions and the integration of specialised services with local aspects of care. For the rest,

⁴²¹ <http://www.raredisease.org.uk/>

⁴²² http://www.raredisease.org.uk/raredisease_strategy_consultation.htm

⁴²³ <http://www.shca.info/PDF%20files/The%20challenge%20of%20rarity%20-%20FINAL.pdf>

⁴²⁴ <http://www.shca.info/PDF%20files/SHCA%20Report%202011%20low%20res.pdf>

⁴²⁵ <http://www.shca.info/PDF%20files/Registries%20Guide%20-%20FINAL.pdf>

the Alliance has been largely focused on seeking to ensure that the major changes in specialised commissioning in England are tailored to the best interests of all those needing specialised care

Genetic Alliance UK

Genetic Alliance UK, formerly the Genetic Interest Group, changed to its new name in 2010. The long-established non-profit group with over 130 member organisations believes the new name - Genetic Alliance UK⁴²⁶ - as well as the updated slogan and logo more accurately reflect the work of the group.

A project supported by Genetic Alliance UK, and facilitated by the Welsh Institute for Health and Social Care, examines the benefit/risk ratio of new medicinal products for rare and serious diseases. The report⁴²⁷ published in 2012 exposes the findings determined by a Citizen's Jury composed of twelve rare and/or serious genetic disease patients or family members, who explored certain key questions: How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines? To what extent should regulators be more permissive in their marketing authorisation decisions? How should patients be involved in the assessment of risks and benefits, and regulatory decision making? After exploring hypothetical case studies and hearing from expert and advocate witnesses on the existing regulatory system and its various strengths and weaknesses, followed by a period of reflection and debate, the jury was able to establish four key recommendations: Regulators should include psychosocial factors in their decision making; Regulators should be more permissive for people with rare and/or serious conditions; Patients should be more involved from setting the research agenda, to post-marketing authorisation decisions; and Patients should be supported in their decision making.

The Northern Ireland Rare Disease Partnership (NIRDP) was formally launched on Rare Disease Day 2012 with support from patients, families, health professionals and government representatives. A non-profit organisation, the NIRDP seeks to bring together rare disease patients and organisations with clinicians and other health professionals, researchers and producers of specialist medicines and equipment, health policy makers and academics to find "...practical ways of improving the quality of life, treatment and care for those with rare diseases in Northern Ireland". The new association will work closely with the Patient Client Council, with other Health and Social Care Agencies in Northern Ireland, with RDUK, IPOSSI, and GRDO in the Republic of Ireland.

Patient organisations are officially recognised thanks to a strong government policy for public and patient involvement (PPI). Hospitals and health services are required to consult their patients about changes to the service and there are continuous surveys a patient experience and patient satisfaction in NHS hospitals. Patient opinion is not binding. In most cases patients' representatives are eligible for reimbursement of expenses.

Amongst the sources of funding available for patient organisations, the government makes funding available to patient organisations through a system known as a Section 64 grant. Many patient organisations have also obtained funding from the National Lottery which is obliged by law to give a percentage of its profits to charitable organisations: activities such as capacity building, networking, dissemination of information, educational events, exchange of best practices, capacity building to improve patients' integration in social environments and outreach to very isolated patients are all eligible for funding by these schemes. Grants are available to support patients' organisations: for example in 2008, the NCG accorded funding to two patient support groups in order to finance clinics in the UK for Alström Syndrome and Ataxia-telangiectasia. This is a novel structure where the clinic is partnered by patient groups, hospitals and the NHS.

Sources of information on rare diseases and national help lines

Orphanet activity in the United Kingdom

Since 2004 there is a dedicated Orphanet team for the United Kingdom (Orphanet UK) hosted at the University of Manchester. This team was officially designated by the Department of Health as the official Orphanet team in the United Kingdom in 2010.

Orphanet UK is in charge of collecting and validating data on rare disease related services (expert centres, medical laboratories, patient organisations, clinical trials, patient registries, mutation databases/ biobanks and ongoing research), in the UK and in Ireland for entry into the Orphanet database. The Orphanet UK team maintains the Orphanet UK national website⁴²⁸ that aims to be an interactive communication tool between the team and the rare disease community. The team represents Orphanet at many major national

⁴²⁶ <http://www.geneticalliance.org.uk/index.html>

⁴²⁷ <http://www.geneticalliance.org.uk/docs/citizens-jury-report.pdf>

⁴²⁸ <http://www.orphanet.co.uk>

conferences and events such as workshops on rare diseases and the Rare Disease Day and it also participates regularly at the ESHG (European Society of Human Genetics) conference. Moreover, Orphanet together with Nowgen hosted the Europlan UK conference meeting on 16 November 2010 in Manchester. Orphanet UK has established collaborations with Dyscerne (A Network of Centres of Expertise for Dysmorpology), Rare Disease UK and Ataxia UK, a charity aiming to support everyone affected by ataxia and fund research into developing treatments. The team also works closely with the National Genetics Reference Laboratory (NGRL) Manchester and has established solid relations with other rare disease organisations such as the Genetic Alliance UK, the British Paediatric Surveillance Unit (BPSU) and the Myrovitis Trust.

Official information centre for rare diseases

There is no official information centre for rare diseases in the UK other than Orphanet.

Help line

There is no official helpline specifically dedicated to rare diseases in the UK but there are national NHS helplines which differ slightly in each of the four countries. In England and Wales the helpline is known as NHS Direct, and in Scotland as NHS 24.

Other sources of information on rare diseases

Information, advice and support are generally provided by patient organisations dealing with particular rare diseases. Some information is provided by NHS websites: <http://www.nhs.uk/>, www.nsc.nhs.uk, www.specialisedservices.nhs.uk, and <http://www.evidence.nhs.uk>.

Contact-a-Family is a key resource for rare diseases. It runs a help line and an online service putting patients in contact with other patients with the same disease (rare or non-rare) and support groups. Other larger patient organisations, both large and small are instrumental in providing information and support. Many run help lines providing general and technical information, provide written information and psychological support: these are funded through various means including donations, fundraising, pharmaceutical companies and grants for the government and other organisations. Many hospitals, especially in the nationally commissioned services also run help lines: these are funded using general health services funds.

UK-based charity Unique⁴²⁹ has been gathering information on specific chromosome disorders for almost 25 years and since 2003 has been producing family-friendly, medically-verified, disorder-specific information leaflets (learn more.) To date, Unique has published over 125 guides on individual chromosomal disorders, which are available free of charge, and frequently in other languages including Dutch, French, German and Spanish. The Unique newsletter reports that for many families, the leaflets are the first concrete source of information obtained for a specific disorder. Now another new guide, entitled After Diagnosis: What Happens Next? The Early Years, targets parents of pre-school children (0 to 4 years) with a rare chromosome disorder and/or global developmental delay. This guide responds to questions relevant to parents of a newly-diagnosed infant everywhere, and also lists resources available in the United Kingdom for affected children and their families.

Good practice guidelines

Nowgen⁴³⁰, a centre of excellence in public engagement, education and professional training in biomedicine, part of the NIHR Manchester Biomedical Research Centre, in collaboration with Dyscerne⁴³¹ has published a portfolio of management guidelines for rare diseases (Angelman syndrome, Kabuki syndrome, Noonan syndrome, Williams syndrome, 22q11 Deletion Syndrome, Achondroplasia, Neurofibromatosis Type 1 & Neurofibromatosis Type 2) using validated methodologies⁴³².

A range of other guidelines for rare and very rare diseases are posted on the NSCT website⁴³³ or published in professional journals.

A guidance document⁴³⁴ on the initial evaluation of paediatric patients with suspected sex development disorders was published in 2011. The free-access article appearing in *Clinical Endocrinology* provides guidance on the initial evaluation of an infant or adolescence with a suspected disorder of sexual

⁴²⁹ <http://www.rarechromo.org/html/home.asp> and <http://www.rarechromo.org/html/LeafletProtocol.asp>

⁴³⁰ www.nowgen.org.uk

⁴³¹ www.dyscerne.org

⁴³² www.dyscerne.org/dysc/Guidelines & <http://www.mangen.co.uk/professionals/clinical-services/useful-documents.aspx>.

⁴³³ www.ncg.nhs.uk

⁴³⁴ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132446/?tool=pubmed>

development. The guidance also evokes the utility of networks and registries to support clinicians, and support groups and psychological services to support the patient and parents.

Training and education initiatives

Nowgen's professional training team delivers a portfolio of training courses that are particularly relevant to healthcare professionals involved in the management and treatment of rare diseases. These include: Antenatal and Newborn Screening; Molecular Genetics for Genetic Counsellors; Molecular Genetics for Cytogeneticists and Bioinformatics for Clinical Geneticists. Many of these courses have included interactive sessions to inform delegates about Orphanet.

National rare disease events in 2012

The UK based charity 'Jeans for Genes' holds an annual awareness day to raise funds for genetic disorders⁴³⁵.

Rare Disease UK and their member organisations planned a number of events to mark Rare Disease Day 2012 across the United Kingdom. This included a contact campaigns aimed at politicians in each of the UK parliaments/assemblies, as well as a specific Rare Disease Day event at Royal Holloway University and a Northern Ireland Rare Disease Partnership event at Stormont Estate where the group launched a report looking into experiences of obtaining a diagnosis of a rare disease in Northern Ireland.

An event entitled, "Rare Diseases in the UK - Vision 2020" was held in Cambridge on 4 July 2012, bringing together to discuss the application of exome sequencing technologies.

Hosted rare disease events in 2012

Amongst the rare disease related events hosted by the UK and announced in *OrphaNews Europe* were: 3rd Annual Orphan Drug Summit (London, 25-26 July 2012), 8th International Prader-Willi Syndrome Conference (Cambridge, 17-21 July 2013), 4th International DSD (Disorders of Sex Development) Symposium (Glasgow, 7-9 June 2013), Translating Genomics Conference (Cambridge, 4 December 2012), Genomic Disorders 2012 (Cambridge, 21-24 March 2012), 13th International Conference on Neuronal Ceroid Lipofuscinosis and 1st Worldwide Meeting of Batten Disease International Alliance (London, 28-31 March 2012), CILIA 2012 - Cilia in Development and Disease (London, 16-18 May 2012), International Ataxia Research Conference (London, 1-3 November 2012), Joint DIA/ EFGCP/ EMA Medicines for Children Conference on Development of Paediatric Medicines: From Learning to Adapting (London, 26-27 September 2012), Orphan Drugs & Rare Diseases Conference (London, 8-9 October 2012), Epidermolysis Bullosa – An Introduction and Advanced Management courses (London, September 2012).

Research activities and E-Rare partnership

National research activities

Rare diseases research has been supported in the UK. Government funding is mostly available through the Research Councils (e.g. the Medical Research Council) and the National Institute for Health Research (NIHR). Many of the NIHR-funded Biomedical Research Centres (BRCs) and Biomedical Research Units (BRUs) undertake translational health research into rare diseases, and in April 2012 a new round of BRCs and BRUs commenced with £800 million investment over 5 years. In addition, as announced in *the Strategy for UK Life Sciences*, the Department of Health is creating a new NIHR BioResource, to provide a national cohort of healthy volunteers, patients and their relatives who wish to participate in experimental medicine research, and are willing to provide clinical information and samples that will enable them to be recalled for specific studies. These studies will have the potential to rapidly advance the understanding of disease mechanisms, identify potential drug targets, and improve insight into the therapeutic potential and limitations of existing and emerging therapies. The BioResource is on track to be launched in early 2014, however it is already supporting translational research into rare diseases, which is one of its 4 themes of focus. On the basis of the research into rare diseases being undertaken in the NIHR, the Department of Health has confirmed NIHR's membership of the International Rare Disease Research Consortium (IRDIRC) this consortium.

There are several major funding charities, particularly for cancer and heart diseases, and a number of rare diseases charities fund research (such as the Muscular Dystrophy Campaign, the Cystic Fibrosis Trust, the Dystrophic Epidermolysis Association etc). Many products for rare diseases have been put through trials in the UK by major pharmaceutical companies (i.e. enzyme replacement therapies, drugs for pulmonary hypertension, etc).

⁴³⁵ <http://www.jeansforgenes.com/about>

In 2012, a new funding mechanism was created by global charitable foundation the Wellcome Trust. The Pathfinder Awards support academic-industry partnerships dedicated to early-stage applied research in the field of rare and neglected diseases. Open to international participation, the Pathfinder Awards seek to kick-start pilot research initiatives showing potential for developing innovative medicinal products for rare or neglected diseases. The first two awards were granted in 2012, both for rare diseases.

In 2012, the Medical Research Council awarded the University of Edinburgh's MRC Human Genetics Unit and the MRC Institute of Genetics and Molecular Medicine £60 million (€74.2 million) in funding over a five-year period to study illnesses and inherited disorders, including cystic fibrosis, retinitis pigmentosa, anophthalmia, and other rare conditions.

Participation in European research projects

British teams participate or have participated in European rare disease research projects including: AAVEYE, ALPHAMAN, ACADEMIC GMP, ANTEPRION, ANTIMAL, BIG HEART, BIOMALPAR, BNE, BALANCE, CARADIOGENET, CHD PLATFORM, CHEARTED, CRUMBS IN SIGHT, CILMALVAC, CLINIGENE, CONTICANET, CELL PID, CSI-LTB, DARTRIX, DSDLIFE, DEMCHILD, EMSA-SG, EUROCRAN, EMVDA, EURADRENAL, ENRAH, EPOKS, EUMITOCOMBAT, EURAMY, EUREGENE, EURO BONET, EUROCARE CF, EUROAGENTEST 1&2, EUROGLYCANET, EURO IRON1, EUROMOTOR, ENCCA, ENS@T, ESPOIR, EUROSARC, EURENOMICS, EUROSCA, EUROTRAPS, EUCILIA, EURO-LAMINOPATHIES, EUNEFRON, EUROPADNET, EUROWILSON, ENCE-PLAN, EVI-GENORET, ESDN, FIGHTHLH, GEN2PHEN, GRIP, GAPVAC, GENEGRIFT, GENESKIN, INHERITANCE, IMMOMEK, INTREALL, INTERPREGGEN, HUMALMAB, LEISHDNAVAX, PWS, MITOTARGET, MPCM, MALARIA AGE EXPOSURE, MABSOT, MITOCIRCLE, MM-TB, MOLDIAG-PACA, MPCM, MYELINET, MYORES, NEUROMICS, NEOTIM, NEUPROCF, NEUROKCNQPATHIES, NEUROPRION, NEUROSIS, PSYCHCNVS, NEWTBDRUGS, OVER-MyR, PADDINGTON, PNSEURONET, PULMOTNESION, PWS, RATSTREAM, STRONG, SPASTICMODELS, RDCONNECT, RAREBESTPRACTICES, RD PLATFORM, STEM-HD, TAMAHUD, TISSUGEN, TIRCON, TAIN, TREAT-NMD, VITAL and THERAPEUSKIN, Biology of cilia formation and intraflagellar transport project, and Relationship of BBS proteins in Wnt pathways project.

E-Rare

The UK is not currently a partner of the E-Rare project.

IRDiRC

The National Institute for Health Research is a committed member of the IRDiRC.

Orphan medicinal products⁴³⁶

The promotion of the development of orphan medicinal products in the UK takes place at a European, and not national, level: orphan medicinal products obtain Marketing Authorisation through the centralised procedure at the EMA. Orphan medicinal products obtain Marketing Authorisation through the centralised procedure at EMA. The body responsible for regulatory approval in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA): accessibility to medicinal products is generally determined by the National Institute for Clinical Excellence (NICE).

Orphan medicinal product committee

The Advisory Group for National Specialised Services (AGNSS) recently developed a new framework for evaluating "ultra-orphan" drugs: ultra-orphan diseases affect less than 500 people in England. Ultra-orphan medicinal products are not subject to NICE appraisals, but to those of the AGNSS: applications are evaluated for clinical desirability on the information received from clinicians on a case-by-case basis⁴³⁷. However, Health Ministers in England announced in 2012 that from April 2013 NICE will take on the role of appraising drugs for ultra-rare conditions, defined as those affecting fewer than 500 patients in England (equating to a prevalence of 1 in 100 000 or fewer).

Orphan medicinal product incentives

No specific incentives reported.

⁴³⁶ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

⁴³⁷ EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl, F. Bachner (2011) p61

Orphan medicinal product market availability situation

No specific information has been provided concerning orphan medicinal products launched on the market in the United Kingdom.

Orphan medicinal product pricing policy

Control of branded manufacturer prices for all medicines is regulated by the Pharmaceutical Price Regulation Scheme which is essentially a profit cap adjusted to the company's capital in the UK. Value-priced pricing will come into effect from 2014 for newly launched branded medicines⁴³⁸.

Orphan medicinal product reimbursement policy

The NHS provides all medicines almost free of charge to all patients: there is a small co-payment ('prescription charge') for out-of-hospital drugs. However the elderly, children and those on low income (and other groups) are exempt from this charge. There is no prescription charge in Scotland and Wales.

Licensed drugs are paid for by the NHS in the UK. Decisions are taken by relevant funding bodies at PCT level, not nationally, in the light of available funds. This has led to criticism that access to drugs can be a "postcode lottery" i.e. access varies widely depending on where an individual lives. The National Specialised Commissioning Team funded certain orphan medicinal products at national level.

Other initiatives to improve access to orphan medicinal products^{439,440}

Orphan medicinal products, like other drugs, are distributed through hospital pharmacies and specialist centres. Home delivery is available for various products, for example enzyme replacement therapies.

Patients with rare diseases can receive unlicensed drugs; in such cases the doctor applies to the MHRA to import it on an individual named patient basis.

The United Kingdom's National Institute for Health and Clinical Excellence (NICE) has launched a consultation process for a new scheme that would permit patients with rare or uncommon disorders to access innovative treatments that have not yet been subject to appraisal by NICE. The NICE "Innovation Pass" will make selected innovative medicines available on the National Health Service for a time-limited period prior to receiving a NICE appraisal. Funding will be drawn from a new ring-fenced £25 million (£27.6 million) budget. The Innovative Pass allows patients earlier access to innovative medicinal products while simultaneously facilitating the gathering of further evidence to "support a subsequent NICE appraisal".

The National Institute for Health and Clinical Excellence (NICE) started to commissioning expert assessments for off-label medicine use from spring 2012⁴⁴¹. These assessments do not constitute formal guidance, but rather provide "a summary of available evidence on selected unlicensed drugs to inform local decision-making". The National Health Service (NHS) in England receives some 1000 specific requests for off-label use annually. The announcement for the off-label product assessments has been met with approval from the rare disease community.

On 18 February 2012 an evidence session was held in the Scottish Parliament a result of the petition sent by Rare Disease UK for the government to address two issues in relation to access to orphan medicinal products in Scotland, namely that the Scottish Medicines Consortium (SMC) appraisal process is not suitable for orphan medicines, and that the Individual Patient Treatment Request (IPTR) process discriminates against patients affected by rare diseases, due to the difficulty in proving exceptionality. Whilst the session was looking at issues of access broadly, access to orphan medicines was also discussed.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

⁴³⁸ Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Access Issues, Donald Macarthur (2011) pp.86-7

⁴³⁹ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

⁴⁴⁰ Written using information from the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p23).

⁴⁴¹ <http://www.nice.org.uk/newsroom/news/BetterInformationOnUnlicensedDrugS.jsp>

Specialised social services

Respite care services are available in most parts of the UK and are provided by the NHS and charitable organisations. Patient groups also organise holiday camps for children and adolescents. Reimbursement varies: all NHS services are free but charities may ask for a small co-payment in some cases. The provision of recreational programmes is patchy but it is difficult to obtain full information: schemes are usually run by individual patient organisations or by local authority social service departments. A small co-payment is usually expected. Services to integrate patients in daily life are the responsibility of local authority social services departments which are government financed.

2. OTHER EUROPEAN COUNTRIES

2.1. CROATIA

Definition of a rare disease

Stakeholders in Croatia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

There is currently no official strategy or plan in Croatia regarding rare diseases. In 2008, the Croatian Society for Rare Diseases⁴⁴² was established as part of Croatian Medical Association, with the aim of preparing a proposal to be presented to governmental authorities (including the parliament and the Ministry of Health and Social Welfare of Republic of Croatia) for the development of a national plan for rare diseases. Since this initiative, the Ministry of Health and Social Care established the National Commission for Rare Diseases in May 2010 in order to elaborate a National Plan for Rare Diseases. This Committee includes three representatives of civil organisations for rare diseases. During 2011 and 2012 the Committee met on the regular basis which resulted in some progress in creating the national plan for rare diseases.

The Croatian national plan for rare diseases is being developed around of the following nine priority areas:

1. Promotion of the knowledge and the availability of information on rare diseases;
2. Support of rare disease registries and securing of their sustainability;
3. Facilitation of referral centres and centres of expertise activities;
4. Improvement of the availability and quality of health services for rare disease patients (prevention, diagnosis, treatment);
5. Improvement of access to treatment with orphan medicinal products;
6. Securing the availability of special social services for rare diseases patients.
7. Empowerment of patient's organisations;
8. Encouraging research activities in the field of rare diseases;
9. International networking in the field of rare diseases.

The draft was presented to the Croatian Society of Patients with Rare Diseases in December 2012 before public consultation and presentation to the Parliament.

The First National Conference on Rare Diseases (17-19 September 2010)⁴⁴³, organised by the Croatian Association for Rare Disorders, under the auspices of the President of the Republic in the scope of the Europlan conference, allowed stakeholders to meet and discuss priorities for the plan. General proposals and guidelines for actions at national level were agreed on by the participants: to improve access to health care and social services, including the protection of patients' social rights and their right to multidisciplinary approach to care; to ensure the introduction of the category of rare diseases in the legal acts of health and social care; to establish a registry for RD and ensure its long term sustainability by providing ongoing funding; to establish a network of Centres of Expertise or a network of physicians working with RD patients; to aid the empowerment and support for patient organisations: to support international networking and cooperation in the field of rare diseases. The Second National Conference on Rare Diseases was held on 8 October 2011. Like the previous conference, it was again the meeting of all national stakeholders. Numerous problems were discussed. The need to strengthen efforts and accelerate the activities to fulfill the goals outlined during the previous conference was emphasised.

There is currently no earmarked budget for rare diseases in the national health care budget, but special funding is available however for orphan medicinal products and there is a "List of Especially Expensive Drugs".

Centres of expertise

There are currently three Referral Centres for rare diseases acknowledged by the Croatian Ministry of Health and Social Welfare: the Referral Centre for Birth Defects (Children's University Hospital Zagreb, Decision UP/I-510.01/02-01/18, No 534-05-01/8-03-10), the Referral Centre for Rare Diseases and Metabolic Disorders

⁴⁴² <http://www.rijetke-bolesti.org>

⁴⁴³ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Croatia_n_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

(Department of Internal Medicine, Clinical Hospital Centre Zagreb; Decision UP/I-510-01/08-01/11, No 534-07-1-2/6-08-12), and the Referral Centre for the Medical Genetics and Metabolic Diseases in Children (Department of Paediatrics, Clinical Hospital Centre Zagreb, Decision UP –I-510-01/95-01/0005, No534-02-10-99-0003). These centres of expertise foster a multidisciplinary approach to rare disease patient care adhering to high medical standards. There are some other centres dealing with particular diseases, for instance the Referral Centre for Haemophilia, Referral Centre for solid tumours in children, etc. The funding and designation of centres of expertise will be a focus of the national plan for rare diseases.

Registries

Currently, there is neither a national registry for rare diseases in Croatia, nor a national committee dedicated to registries for rare diseases nor designated registries for rare diseases. However, many patients are registered through the mentioned referral centres and patient organisations (phenylketonuria, other inborn errors of metabolism in children, Prader-Willi syndrome, osteogenesis imperfecta, epidermolysis bulosa, etc.) or international on-line registries. These types of registries are not financed. The exception regarding financing is the E-IMD registry for urea cycle defects and some organic acidurias which is part of the EC financed E-IMD project. As a part of EUROCAT network of congenital anomaly registries, Zagreb Registry covers four regions of Croatia (17% of annual births) and this initiative was extended during 2011 to two new regions. This activity is funded as a part of Joint Action EUROCAT 2011-2013 by the Public Health Programme 2008-2013 of the European Commission. The establishment of the National EUROCAT Committee is in progress. A project to develop epidemiological data on patients with rare tumours in Croatia via a registry is underway in collaboration with the Croatian patient organisation for cancers “Za novi dan”. Croatia also contributes to the European registry EUROCAT, EUROCAT CF, PID, European registry for intoxication type metabolic diseases (E-IMD) and TREAT-NMD.

Neonatal screening policy

Neonatal screening is centralised in Croatia and is an obligatory part of health care. Neonatal screening is provided for phenylketonuria and hypothyroidism. In addition, in 2003 national screening for hearing impairment was implemented and covers the whole of the country. Preliminary activities to extend the newborn screening program by tandem mass spectrometry are underway. The national screening laboratory has been renovated and equipped with tandem mass spectrometry equipment. The remaining problems to extend the screening are to clarify legislation and funding of the running costs.

Genetic testing

Genetic testing is available for the most common genetic conditions in laboratories of clinical hospitals or research institutes. Genetic testing is covered by the Croatian Institute for Health Insurance: when a certain test is not available in Croatia, a second medical opinion from 2-3 medical professionals is needed before a sample can be sent abroad. However there are still some problems with these sorts of cross-border services.

Diagnostic tests are registered as available in Croatia for 28 genes and an estimated 38 diseases in the Orphanet database⁴⁴⁴. According to data from Croatian Society of Human Genetics testing is available for 48 genetic disorders (some laboratories are not listed yet in Orphanet database). There are no national guidelines for genetic tests although there have been activities of Croatian Society for Human Genetics in this sense.

National alliances of patient organisations and patient representation

Since its registration as a non-profit humanitarian organisation in April 2007, the Croatian Society of Patients with Rare Diseases⁴⁴⁵ has been working on developing relations with the stakeholders who have an impact on the lives of patients with rare diseases. The Society works to raise general awareness concerning rare diseases and lobbies political stakeholders. The Croatian Alliance for Rare Diseases, replacing the Croatian Society of Patients with Rare Diseases was established in 2012 as the umbrella organisation for rare diseases that gathers 14 other non-profit organisations and more than 200 patients with rare diseases and members of their families who do not have patient organisation representation. At present there are more than 110 different rare diseases registered in the association.

Patient organisation activities are supported by the government and other non-governmental bodies: this financial support is intended for capacity building, networking activities, dissemination of information and information sharing and events.

⁴⁴⁴ Information extracted from the Orphanet database in December 2012.

⁴⁴⁵ <http://www.rijetke-bolesti.hr>

Representatives of patient organisations are also invited to participate in the meetings of the Croatian Society for Rare Diseases when policy issues (and other issues of interest are discussed). Financial support is available for patients to attend these meetings. Most patient organisations' boards usually include a medical professional involved with patients in consultations, policy making etc.

Sources of information on rare diseases and national help lines

Orphanet activities in Croatia

Since 2006, there is a dedicated Orphanet team in Croatia, currently hosted by the Zagreb University School of Medicine. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. There is an Orphanet national website which was launched in 2012⁴⁴⁶.

Official information centre for rare diseases

Apart from the national Orphanet team there is no official information centres on rare diseases in Croatia. However, from 2011 the new office of the Croatian Society for Rare Diseases, part of the Croatian Medical Association, started to function as an information centre, financed primarily by donations. This service has the support of the government and is consulted by governmental institutions, but it is not designated as an official information centre.

Help line

A rare disease helpline was established in Croatia in 2012 by the Croatian Alliance for Rare Diseases. It will be financed through the project and by donations. Informal help lines run by patient organisations provide general information for rare diseases diagnostic and management.

Other sources of information

Information on rare diseases is provided by the Croatian Society for Rare Diseases and by institutions hosting the mentioned referral centres. There are also certain public information sources on rare diseases, including help lines and websites run by patient organisations and non-governmental organisations. The site run by the Croatian Society of Patients with Rare Diseases (<http://www.rijetke-bolesti.hr/>) includes information on certain diseases and groups of diseases. The Croatian Society for Rare Diseases has developed a website which contains comprehensive information for professionals and patients (www.rijetke-bolesti.org).

Good practice guidelines

No specific activity reported.

Training and education initiatives

Current university training courses do not yet provide specific training on rare diseases. Information on rare diseases is included in curricula for medical students, students at Faculty of Education and Rehabilitation Sciences and students at Faculty of Pharmacy and Biochemistry, University of Zagreb.

National rare disease events in 2012

To mark Rare Disease Day 2012, a symposium on rare diseases took place on 24 February 2012 at Hotel Dubrovnik in Zagreb, organised by the Croatian Society for Rare Diseases of the Croatian Medical Association. In addition, information stands were present in Zagreb on 25 February 2012, an event attended by the Mayor of Zagreb, and other events took place the same day in Osijek, Rijeka, Split and Dubrovnik. On 29 February 2012 representatives from rare disease patient organisations dealing with rare diseases held a meeting with the Minister of Health Rajko Ostojić at the Ministry of Health, and educational events were held at the Zagreb Health School.

In collaboration with the European Organisation for Rare Diseases (EURORDIS) and the City Office for Health and War Veterans; under the auspices of the Croatian President Prof. Ivo Josipovic and with the support of the Croatian Medical Students' International Committee (CroMSIC) and the Coalition of Healthcare Associations, the events were held in six cities: Krizevci, Osijek, Rijeka, Split, Dubrovnik and Zagreb.

Hosted rare disease events in 2012

No events reported in OrphaNews Europe.

⁴⁴⁶ <http://www.orpha.net/national/HR-HR/index/homepage/>

Research activities and E-Rare partnership

Research activities

There are around 40 projects funded by the Ministry of Science, Education and Sports for the investigation of genetic diseases and various other groups of rare diseases. Some pharmaceutical companies involved in the management of rare diseases support investigations of specific rare diseases. There is a database of clinical studies in Croatia (www.regpok.hr) in the Croatian language. New grants from the Croatian Ministry of Health are expected in 2013.

Participation in European research projects

Croatian teams participate, or have participated, in European research projects on rare diseases, including: EUROGLYCANET, European registry and network for intoxication type metabolic diseases, and EUROPEAN LEUKEMIA NET.

E-Rare partnership

Croatia is currently not an E-Rare partner and has not yet participated in these calls.

IRDIRC

Croatian funding agencies have not yet committed funding to IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

In Croatia there is no orphan medicinal product committee, although the Croatian Health Insurance Institute has a drug committee which controls drug use and makes any drug available if approved after individual request by selected national experts.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

The availability of orphan medicinal products has been improved since the establishment of the Fund for Especially Expensive Drugs at the Croatian Institute for Health Insurance, and a regulation for orphan medicinal products is being prepared by a working group to be presented to the Ministry of Health and Social Care.

A tender for drugs for rare diseases was introduced in 2009. This resulted in introduction of only one drug for the treatment of a certain disease, for example for Fabry disease this is agalsidase alfa, whilst agalsidase beta was put on the hospital budget. This caused problems for patients treated with agalsidase beta, as hospital management has asked treating physicians to change the treatment to agalsidase alfa. These problems have later been solved. In 2012 Croatian Institute for Health Insurance released an update (Decision, 2012, May 24) of the List of Especially Expensive Drugs which includes drugs for several rare diseases (drugs for multiple sclerosis, some cancers, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, home treatment of hemophyllia, peginterferon, growth hormone, enzyme replacement therapy). Orphan medicinal products approved for treatment of rare and severe diseases can be found on the web pages of the Croatian Agency for Drugs and Medicinal Products⁴⁴⁷. There is a detailed procedure regulating the inclusion of a drug on the List of Especially Expensive Drugs. The final decision is taken by the Board of the Croatian Institute for Health Insurance, based on the report of Committee for drugs and medicinal products.

Orphan medicinal product pricing policy

No specific activity reported.

Orphan medicinal product reimbursement policy

In Croatia, treatment for rare diseases was originally covered using the hospitals' budget and hospitals were reluctant to begin a therapy presenting such a heavy financial burden. After a long negotiation between patients' organisations and professionals involved in the treatment of rare diseases with authorities, the Ministry of Health established in 2006 a "List of Especially Expensive Drugs" (Legislative Decree Class: 025-04/06-01/91, No: 338-01-01-06-1, Zagreb, 9. March 2006.) and the treatment of rare diseases is now covered from specially allocated funds from general state health system budget. Orphan medicinal products are thus

⁴⁴⁷ www.halmed.hr

now approved by the Croatian Institute for Health Insurance: all available orphan medicinal products are reimbursed by the Croatian health insurance fund (“expensive drug fund”) for rare diseases.

In 2010 the Croatian Institute for Health Insurance has introduced a regulatory method for the control of the consumption of drugs that are on the “List of Especially Expensive Drugs”. Maximal spending budget is regulated by the 3-year contracts and monitored monthly. This policy sometimes makes difficult ensuring prompt treatment for newly discovered patients.

Other initiatives to improve access to orphan medicinal products

Compassionate use is possible from the time of diagnosis to the approval for the use of the drug. The importation of relatively cheap drugs is sometimes problematic, because there is no obligation for companies to provide the drug.

Other therapies for rare diseases

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

There are possibilities for different types of social and respite care services in some parts of the country, although not specifically for rare disease patients, but for those affected with chronic disorders in general: these services are fully reimbursed by national health care. Therapeutic recreational programmes such as summer camps are organised by patient organisations (e.g. children’s camps for those affected by rare forms of solid tumours and lymphomas): this is fully reimbursed by the patient organisation. Social and/or financial support for families and patients with disabilities is regulated by a number of legislative decisions/regulations. Fostering of employment for the integration of handicapped individuals in daily life is partly financed by the government. Recently the National Strategy for Equal Possibilities for Handicapped Individuals 2007-2015 (Class 562.01./07-01/02, No 5030108-07-1, June 2007) was introduced in order to regulate the area of services aimed at the integration of patients with handicaps in daily life. In 2012, there were no new initiatives in the field of respite care.

2.2. ICELAND

Definition of a rare disease

In Iceland a condition is defined as rare if it affects 2 or fewer individuals per 10 000.

National plan/strategy for rare diseases and related actions

In Iceland there is not yet a specific plan for rare diseases. In 2012, for the first time, Iceland was able to send a representative to a EUCERD meeting, which already has increased discussion and awareness of rare diseases in Iceland at the level of the Ministry, stakeholders and rehabilitation services. Representatives from these organisations now meet regularly with the purpose to increase awareness of rare diseases within the country. A strategy for disabilities was launched in 2012 and the plan is to revise this document next year and include a chapter on rare diseases within it. Currently, there is no specific funding in place for rare diseases. In 2012 Iceland hosted a Nordic meeting on rare diseases with 120 attendees from all the Nordic countries.

Centres of expertise

Up to now, no centres in Iceland have been designated as national centres of expertise. However, since 1986 one national habilitation centre provides services for children and adolescents with conditions leading to disability, including rare diseases and syndromes. The same accounts for diagnostic and habilitation services for visually impaired and hearing impaired children and adults including those with rare diagnosis. These services are centralized at two national centres. Administrative databases designed to collect and store data on causes of disability (including rare diseases/syndromes) are developed at these three centres and updated regularly. The plan is to further enhance services for individuals with rare diseases at these centres.

Registries

In Iceland there is no formal national committee dedicated to dealing with registries but administrative databases (see above) are organized by directors of the individual national centres. In 2012, a centralised database on causes of deaf blindness (combined hearing and visual impairment) among Icelandic children and adults was established in cooperation of these three national centres servicing people with disabling conditions. These administrative databases are financed by the state. In addition, Icelandic teams contribute to the EURO CARE CF and RARE CARE European registries.

Neonatal screening policy

There have not been any developments in the neonatal screening policy in 2012 nor have there been additions to the list of rare diseases tested. Since 1 January 2008 neonates in Iceland have been screened for 42 different rare diseases using tandem mass spectrometry.

Genetic testing

Genetic testing (as well as genetic counseling) in Iceland is centralised at the Department of Genetics and Molecular Biology of the National University Hospital of Iceland. Other than guidelines regarding the newborn screening, Iceland does not have national guidelines regarding genetic testing. Genetic testing abroad is possible as specimens are frequently sent abroad for further testing which is not possible to perform in Iceland. The patients pay only a small proportion of the total cost of genetic testing (universal health care) but there are no specific provisions in place for patients with rare diseases.

National alliances of patient organisations and patient representation

In Iceland there is one patient organisation focusing on children with rare diseases and their families. The organisation is called "Unique children". In 2012, collaboration was initiated between representatives from the organisation "Unique children", the Ministry of Welfare and the national habilitation centre with the aim to increase awareness of rare diseases at all service levels in the country.

Sources of information on rare diseases and national help lines

Orphanet activities in Iceland

There is no Orphanet team in Iceland.

Official information centre for rare diseases

In Iceland there is no official information centre for rare diseases. However, the patient organisation, Unique Children, provides information regarding rare diseases and the Nordic cooperation Rarelink (with its Icelandic link, www.rarelink.is) provides information on hundreds of rare diseases (either in the Nordic languages or English). Rarelink also offers networking for people with rare diseases i.e. people can get information on others within the Nordic countries with the same diagnosis. The organisation Unique Children is not funded by the state but by donations and specific fundraising activities.

Help line

There is no rare disease specific helpline in Iceland.

Other sources of information

Iceland has taken part in Nordic activities regarding rare diseases during the past several years. In autumn 2011 the homepage www.rarelink.is was launched and in 2012 information regarding several rare diseases and syndromes was translated into the Icelandic language and published on this website.

Good practice guidelines

Best practice guidelines for rare diseases have not been produced in Iceland.

Training and education initiatives

No rare disease specific or related training/education courses were held in 2012.

National rare disease events in 2012

The patient organisation "Unique children" celebrated Rare Disease Day for the first time in 2012. The main event was the fund raising event "Rare Run" where people ran a certain distance and raised money for the

organisation. In the radio there was an hour long program dedicated to children with rare diseases. In the program children were interviewed and their favourite songs were played.

Hosted rare disease events in 2012

On 31 May and 1 June 2012 Iceland hosted a Nordic meeting on rare diseases with 120 attendees from all the Nordic countries⁴⁴⁸.

Research activities and E-Rare partnership

Research activities

There are no specific programmes for rare diseases research in Iceland and there are not any fund-raising initiatives for rare diseases research in Iceland.

Participation in European research projects

Icelandic teams participate, or have participated, in European research projects on rare diseases, including: INTERPREGGEN, GEN2PHEN, PSYCHCNVS, EPINOSTICS, EURORETT, EUROSPA, ERCUSYN, and RARECARE.

E-Rare partnership

Iceland is currently not an E-Rare partner and has not yet participated in these calls.

IRDIRC

Icelandic funding agencies are not yet committed members of IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

In Iceland there is no orphan drug committee and there are no official plans to introduce one.

Orphan medicinal product incentives

No specific information reported.

Orphan medicinal product market availability situation

No specific information reported.

Orphan medicinal product pricing policy

No specific information reported.

Orphan medicinal product reimbursement policy

No specific information reported.

Other initiatives to improve access to orphan medicinal products

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

A new information centre for children with rare disease and their families was opened in autumn 2012. The centre is called Leiðarljós (Guiding Light) and offers parents of children with rare diseases nursing support and detailed information regarding available services.

⁴⁴⁸ <http://www.greining.is/media/nordic-conference-2012/nordicconference2012linkar.pdf>

2.3. ISRAEL

Definition of a rare disease

There is no official definition of rare diseases in the legislation and regulations in Israel.

National plan/strategy for rare diseases and related actions

There is currently no national plan for rare diseases in Israel. The costs related to these diseases are included in the national health care budget. There is no funding for action in the field of rare diseases. The Parliament lobby for rare diseases was founded in 2009; a law concerning rare diseases has been submitted to the Parliament for consideration but was rejected.

Centres of expertise

There is a Ministry of Health policy to develop centres of expertise for rare diseases. There are several centres in Israel recognised for providing expert services in the field of rare diseases including, the National Multidisciplinary Clinic for Prader Willi Syndrome, and the Hereditary Hemorrhagic Telangiectasia HHT Clinic.

Registries

Several registries are maintained in Israel including a cystic fibrosis registry and a registry of genetic syndromes causing bone marrow failure. Other registries are planned. At the moment there is not governmental financing for these registries.

Teams in Israel contribute to the EUROCARE CF and SCNIR European registries.

Neonatal screening policy

In Israel, all newborns are screened for 9 rare metabolic diseases and 2 endocrine diseases. All activities related to these tests and quality control is carried out under the supervision of the Ministry of Health.

Genetic testing

The Medical Genetics Association has published guidelines for prereproductive genetic population genetic screening. All these screening tests will be provided free from the beginning of 2013 including cystic fibrosis, SMA and fragile X. Many of the tests are reimbursed (specific mutation testing or linkage, prenatal chromosomal microarray), sequencing of genes and postnatal chromosomal microarray begun to be reimbursed but there are still many of the patients that need to pay for these tests privately. Genetic testing in the private labs in Israel and abroad is possible, but in most cases are not reimbursed and patients pay for these tests privately. In the Orphanet database, 233 genes are tested in Israel for 258 diseases⁴⁴⁹. Private testing for any known disease-causing gene is available in private labs.

National alliances of patient organisations and patient representation

There is no alliance for rare diseases, although there is a non-rare disease specific patient alliance in Israel who is taking action to promote various themes related to Rare Diseases. Representatives of patients with rare diseases have recently met with the General Manager of the Ministry of Health and discussed their problems with him.

Sources of information on rare diseases and national help lines

Orphanet activities

The Orphanet Israel country coordinator is currently based at the Schneider Children's Medical Center of Israel. Orphanet Israel does not currently receive national or European funding. The representative collects data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) for entry into the Orphanet database. This activity is not systematic and is based on the free time of the representative. Orphanet has been officially recognised by the Israeli Ministry of Health. The Orphanet team maintains the Orphanet Israel national website⁴⁵⁰ in Hebrew.

Official information centre for rare diseases

No specific information reported.

⁴⁴⁹ Information extracted from the Orphanet database (December 2012).

⁴⁵⁰ <http://www.orpha.net/national/IL-HE/index/%D7%93%D7%A3-%D7%94%D7%91%D7%99%D7%AA-%D7%A9%D7%9C-%D7%90%D7%95%D7%A8%D7%A4%D7%A0%D7%98-%D7%99%D7%A9%D7%A8%D7%90%D7%9C/>

Help line

No specific information reported.

Other information on rare diseases

There is some publicly open information on rare diseases in Israel available on the Community Genetics Department at the Ministry of Health Website and at the Israeli site at the Goldenhelix mutation database. Web-based information is available for a limited number of diseases and certain information is maintained using a state budget.

Good practice guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

National rare disease events in 2012

On Wednesday, February 29 2012, the Second National Conference was held to mark the International Rare Disease Day, organised by Orphanet Israel, at the Felsenstein Medical Research Center of the Schneider Children's Medical Center of Israel (SCMCI). Around 300 people participated in the conference including physicians, nurses, social workers, researchers and patients. Dr. Zelina Ben-Gershon, Office of the Chief Scientist, Ministry of Health, closed the conference speaking about the importance of promoting research of rare diseases and the necessity for public funding for the recognition of diagnostic characteristics of such diseases in order to develop treatment and cures, since the patients and researchers are few and scattered in different places and therefore cooperation and multinational coordination are essential. The conference successfully presented the topic of rare diseases from a variety of disciplines and points of view, and raised public awareness about the changes taking place in the diagnosis and possible treatment of rare diseases and emphasised the need to examine the entire system for changes and to prepare for them.

Hosted rare disease events in 2012

No specific information reported.

Research activities and E-Rare partnership

National research activities

There are fund-raising initiatives by specific patient organisations for various rare diseases such as familial dysautonomia, ALS, etc.

Participation in European research projects

Teams from Israel participate, or have participated, in a number of European research projects, including: ALS-degeneration, EMSA-SG, SIOPEN-R-NET, ANTEPRION, AUTOROME, COQ-iPSC, CELL PID, CLINIGENE, EUGINDAT, EUROCARE CF, EUROGLYCANET, EURO-IRON1, EUROPEAN LEUKEMIA NET, EMINA-2, GAPVAC, GENOMIT, LEISHMED, MYASTAID, MYORES, NEUROPRION, PWS, STEM-HD, EUROTRAPS, FIGHT-MG, LEISHDRUG, MYELINET, NEURO.GSK3, NEUROSIS, NGIDD, ELA2-CN, EUROGEBETA, PPPT-MJD, INTREALL, OCTIPS, RHORCOD, RARE-G, STRONG, TRANSPSMART, SKINDEV.

E-Rare

Israel is part of the E-Rare consortium, represented by the CSO-MOH (Ministry of Health) and participated in the first two transnational calls in 2007 and 2009 (Israel is represented in three of the selected projects in the first two calls). Israel participated in the third call in the context of E-Rare2 in 2011 and funds Israeli teams participating in 4 of the selected consortia. Israel also participated in the 4th Joint Transnational Call in 2012, with teams from Israel participating in 4 out of the 11 projects selected for funding.

IRDiRC

The CSO-MOH as member of the E-Rare Group of Funders joined the IRDiRC in 2012.

Orphan medicinal products

Currently in Israel there is no agreed definition of an Orphan disease or drug. In addition, there is no special legislation regulating the development registration and payment for orphan medicinal product therapies. Thus these products and patients find themselves competing with general diseases, to their disadvantage.

Orphan medicinal product committee

There is currently no such committee. Attempts to reform the law and regulations have thus far not succeeded, but a draft law is currently going through the Parliament.

Orphan medicinal product incentives

No specific information reported.

Orphan medicinal product market availability situation

All new drugs (including orphan medicinal products) must be registered with the Ministry of Health. The pharmaceutical division has regulations regarding the registration of new drugs, similar to those of the EUMA and FDA. There is no comprehensive list of orphan medicinal products available.

Orphan medicinal product pricing policy

No specific information reported.

Orphan medicinal product reimbursement policy

Public bodies (hospitals, health funds) will only pay for drugs that are financed by the government within the framework of the National Health Insurance Law of 1995. Each year a special committee examines which drugs and technologies will be publicly financed (the "basket of services"). The committee is composed of representatives of all the relevant stakeholders and interested parties. Since budgets are limited, this process of selection is always controversial. More products are proposed than are accepted and the process is complex, competitive, and not entirely transparent. Nevertheless, some orphan medicinal products have been accepted in recent years (e.g. Cerezyme, Kuvan, carglumic acid, nitisinone and miglustat)

Other initiatives to improve access to orphan medicinal products

A "compassionate" procedure ("Form 29g") exists by which life-saving products may be given to individual patients on the responsibility of the treating physician, even if the drug is not registered, or is off-label, or is not included in the basket. However, obtaining such products and paying for them is problematic.

Other therapies for rare diseases

No specific information reported.

Orphan devices

A draft law on this subject has been proposed.

Specialised social services

No specific information reported.

2.4. NORWAY

Definition of a rare disease

In Norway a medical disorder is considered rare when there are less than 100 known cases per million inhabitants. In Norway this corresponds to fewer than 500 known cases. Some medical disorders with a higher prevalence may also be considered rare if only a small number of people have been diagnosed or because of scarcity of knowledge among service providers.

National plan/strategy for rare diseases and related actions

There is ongoing political and practical activity in the field of rare disorders in Norway. Services for people with rare disorders and their families was an area of priority in the government's early plans of actions for the disabled (1990-1993 and 1994-1997). In the following years these action plans have been implemented, followed up and developed to meet current needs.

As users of long-term, coordinated health care and/or social services, patients are entitled to an Individual Plan, which is a personal overall plan for service provisions. Particularly relevant to rare disorders patients, and not conditional on any particular diagnosis or age, this plan will contain an outline of the objectives, resources and the services the patient requires. Despite the various resources available to rare disease patients in Norway, a study reveals that more specialist knowledge is needed, along with an "integrated approach" to health care.

In 2008, the Regional Health Authorities (RHA) initiated a revision of the current national resource functions (including the resource centres for rare disorders). The aim was to identify in a five year perspective which centres of expertise are needed and where in the specialist health services they should be placed. The revision suggests a complete review of the system and services directed to patients with rare disorders. This also includes the distribution of allocated resources. One of the main goals is to facilitate the expansion of the services to include a wider range of rare disorders.

In 2010 the Ministry of Health requested a report on how to reorganise the centres for rare disorders under one administration. The working group led by the Directorate of Health delivered the report⁴⁵¹ on 1 December 2010. The Directorate, with some following remarks, supported the recommendations. In March 2012 the Ministry announced that the South-Eastern Norway Regional Health Authority (SE-RHF) should establish a national competence service for rare diagnosis and disabilities to administrate all the national services in this field today, except the services for dual sensory impairment (for which there is established a new national service at Northern Norway Regional Health Authority). The SE-RHF chose to establish a project in 2013, to organise the unit from 1 January 2014

In addition to this the Regulation on "Approval of hospitals and national services"⁴⁵², which includes centres of expertise for rare disorders, was enforced from the start of 2011: this Regulation imposes the same criteria and demands on centres of expertise for rare disorders as on other national centres of expertise. The document has been translated to English and published⁴⁵³.

Centres of expertise

National competence service

In Norway there are now 10 different state-financed centres of expertise for people with rare and less known disorders. They provide services for more than 16 000 persons with more than 320 different rare disorders, which often lead to disability. As mentioned, these centres will be under one administration from 1 January 2014. In order for a service to be established for a rare disease, the condition must meet the criteria of being complex and compound, and there must be a need for multidisciplinary and cross-institutional services. These centres also facilitate the development and dissemination of expertise, and they provide forms of support unmet by standard services. The centres are administered under the South Eastern Norway Regional Health Authority as specialist health care services. The grants to the centres are earmarked to the RHA through the state budget. The centres report to the Regional Health Authority and to the Directorate for Health. See section 4, §4-5 and §4-6 in the above-mentioned regulation for requirements and responsibilities for the national competence services. §4-3 and §4-4 regulate requirements and responsibilities for national and multi-regional treatment services.

In 2013 a project is funded for the organisation of one administrative body for the units dealing with rare diseases. This unit will be located at Oslo University Hospital. The services will be evaluated through annual and five-year reports.

There are several departments of medical genetics in Norway. Genetic counselling and genetic testing is available on demand as public health care services. In Norway many specialised health care services (e.g. surgery and specialised medical treatment) are centralised to one or a few units in addition to the Centre of Expertise. This is specified in the guide to the regulation mentioned above⁴⁵⁴.

⁴⁵¹ http://www.helsedirektoratet.no/vp/multimedia/archive/00316/Revidert_rapport_Sa_316599a.pdf

⁴⁵² <http://www.regjeringen.no/upload/HOD/SHA/forskrift-eng-270911.pdf>

⁴⁵³ Unofficial translation: <http://www.regjeringen.no/upload/HOD/SHA/forskrift-eng-270911.pdf>

⁴⁵⁴ http://www.regjeringen.no/upload/HOD/SHA/Veiledernasjonale_tjenester01022013b.pdf

Registries

Each national resource centre has its own registry: they report to their respective Regional Health Authority, as well as to the Directorate of Health. Public Health Registries also exist (such as the medical birth registry, cause of death registry, national patient registry and social security registry). Norway contributes to the EURADRENAL, EUROCAT, EPR (European Porphyria Registry), HUE-MAN, SCNIR, RARECARE and EUROCARE European registries.

Neonatal screening policy

Neonatal screening for phenylketonuria and congenital hypothyroidism, as well as newborn hearing screening, has been in place for several years. A report presented to The Norwegian Directorate of Health in March 2009, suggested an expansion to include biochemical screening for in total 23 different conditions. The Government concurred with the recommendations and sanctioned in October 2010 newborn screening for the following conditions: Propionic acidemia, Methylmalonic acidemia, Isovaleric acidemia, Holocarboxylase synthetase deficiency, Biotinidase deficiency, β -Ketothiolase deficiency, Glutaric acidemia type I, Medium-chain acyl-CoA dehydrogenase deficiency, Long-chain L-3-Hydroxy dehydrogenase deficiency, Trifunctional protein deficiency, Very long-chain acyl-CoA dehydrogenase deficiency, Carnitine uptake defect, Carnitine palmitoyltransferase I deficiency, Carnitine palmitoyltransferase II deficiency, Carnitine acylcarnitine translocase deficiency, Glutaric acidemia type II, Maple syrup urine disease, Homocystinuria, Phenylketonuria, Tyrosinemia type I, Congenital adrenal hyperplasia, Congenital hypothyroidism and Cystic fibrosis.

The expansion of the program was to be implemented following a revision of the legal regulation on genetic testing. The new regulation was sanctioned in December 2011 with effect from 1 January 2012. Under this regulation, prior to newborn screening, it is expected that the parents are well informed about tests, methods and possible consequences. Information brochures to parents were produced in close collaboration between The Directorate of Health and Oslo University Hospital before the program was launched on 1 March 2012. Screening is to be based on informed consent, and residual samples may be kept in a diagnostic bio bank for 6 years. Consent is also required for later use of demographic data, analytical results and information related to diagnostic follow-up and treatment. This information will be stored in a quality register for evaluation of the screening program. Parents can decline storage or use of remaining samples in research. In general, use of screening samples in research will require an approval from an ethical committee and a signed agreement from the parents.

Genetic testing

The portal <http://www.genetikkportalen.no> gives an overview of the genetic tests/analysis available in Norway at any time. The portal is administered through Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway. When there is no test available in Norway, samples are sent to laboratories abroad.

Diagnostic tests are registered as available in Norway for 116 genes and an estimated 133 diseases in the Orphanet database⁴⁵⁵.

National alliances of patient organisations and patient representation

There is currently no alliance of rare disease patient organisations in Norway, but the Norwegian Federation of Organisations of Disabled People (FFO) is recognised as the co-ordinating body for organisations of disabled people, including many rare disease patient organisations. The government contributes financially to many patients organisations. There must be at least 250 members in an organisation to qualify for government co-funding. The Directorate of Health initiated a project in 2009 (which has since been finalised) to bring together smaller organisations in order to qualify for financial support, as organisations with less than 250 members may merge with others in order to qualify for government financial support. The Norwegian Directorate for Children, Youth and Family Affairs (BUFdir) is now considering to change the regulations on governmental support to patient organisations, e.g. to make it possible for people with rare disorders and their family to establish organisations.

⁴⁵⁵ Information extracted from the Orphanet database (December 2012).

Sources of information on rare disorders and national help lines

Orphanet activities in Norway

Since 2006 the national coordinator for Orphanet in Norway is based at the Norwegian Directorate of Health and is in charge of collecting data on rare disease related services for entry into the Orphanet database. The Orphanet Norway⁴⁵⁶ national website in Norwegian is maintained by the coordinator.

Official information centres for rare diseases

The centres of expertise develop and revise professionally reviewed information about the different syndromes for which they provide services⁴⁵⁷. This information is published on their websites and in paper copies, often available on site at the Centres from staff dedicated to informing patients and family members.

Help line

Since 1999, the Norwegian Directorate of Health services a free help line for rare disorders. To date, the help line has answered calls for about 850 different rare disorders.

Other sources of information

The Directorate's website makes publications concerning rare diseases available to the public. Norway is also part of Rarelink (www.rarelink.no), a Nordic website which contains a compilation of links to information on rare disorders, published by organisations commissioned by the governments of Sweden, Finland, Denmark and Norway. Another important sources of information is the Directorate's website⁴⁵⁸ and the site for the project to establish a new national unit for administration of the centres of expertise⁴⁵⁹.

Good practice guidelines

The centres of expertise are involved in the preparation and implementation of guidelines and guides for rare disorders.

Training and education initiatives

Several of the national competence services are involved in different educations and training, such as medical schools, odontology training, nursing schools etc. Some centres administrate web-based courses for specific diseases⁴⁶⁰.

National rare disease events in 2012

There are meetings organised at all the resource centres, and annual contact meetings between each centre and their respective regional health authority. Conferences and congresses are organised on special occasions such as Rare Disease Day.

A conference⁴⁶¹ was organised to mark Rare Disease Day at the Norwegian Directorate for Health on 29 February 2012. The event welcomed all stakeholders and several of the Norwegian Centres of Expertise (or rare disorders attended and provided information via stands

Hosted rare disease events in 2012

Amongst the hosted events in 2012 announced in *OrphaNews Europe* was the 1st European Conference on Aniridia (Oslo, 8-10 June 2012).

Research activities and E-Rare partnership

National research activities

National centres of expertise are involved in a number of research projects on rare disorders.

Participation in European research projects

Norwegian teams participate/participated in European rare disease research projects including: ALPHAMAN, CHEARTED, ECFR, EUROCRAN, EURAPS, EURADRENAL, EUROBONET, FNAIT, INTERPREGGEN, INTERALL, HUE-MAN, MYELINET, NEUROXSYS, NEUROKCNQPATHIES, SIOPEN-R-NET and VITAL.

⁴⁵⁶ <http://www.orpha.net/national/NO-NO/index/kort-om-orphanet/>

⁴⁵⁷ Accessible on these sites amongst others <http://www.sjeldnediagnoser.no/> and <http://www.frambu.no/>

⁴⁵⁸ <http://www.helsedirektoratet.no/helse-og-omsorgstjenester/sjeldne-tilstander/Sider/default.aspx>

⁴⁵⁹ <http://www.oslo-universitetssykehus.no/aktuelt/prosjekter/Sider/sjeldne-og-lite-kjente-diagnoser-og-funksjonshemninger-nasjonale-kompetansetjenester-for-.aspx>

⁴⁶⁰ <http://www.sjeldnediagnoser.no/?k=sjeldnediagnoser/home&aid=10960>

⁴⁶¹ <http://www.helsedirektoratet.no/Om/kurs-konferanser/Sider/en-sjelden-dag-2012.aspx>

E-Rare partnership

Norway is not currently a partner of the E-Rare project.

IRDIRC

Norwegian funding agencies have not yet committed funding to the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

There is no orphan medicinal product committee in Norway.

Orphan medicinal product incentives

As an EFTA/EEA member, the EU orphan medicinal product regulation is fully implemented in the EEA agreement, including the orphan designation incentives. As yet no additional national program has been put in place for granting incentives specifically for the development of orphan medicinal products.

Orphan medicinal product market availability situation

By the end of December 2012, 48 orphan medicinal products were marketed in Norway. These drugs are: Aldurazyme, Arzerra, Atriance, Busilvex, Ceplene, Cystadane, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Firazyr, Gliolan, Increlex, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Nexavar, Nplate, Orfadin, Pedeia, Plenadren, Revatio, Revlimid, Revolade, Savene, Signifor, Soliris, Sprycel, Tassigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Wilzin, Xagrid, Xaluprine, Yondelis and Zavesca. Other orphan products with an EEA marketing authorisation, but not yet marketed in Norway, can nevertheless be readily dispensed by the pharmacy when a doctor provides a specific medical prescription form.

Orphan medicinal product pricing

Norway has a structured system for pricing, and orphan medicinal products follow these overall principles.

Orphan medicinal product reimbursement

Norway has an extensive reimbursement system for pricing and reimbursement, and orphan medicinal products follow these overall principles outlined in Article 3 "Blåreseptforskriften". The payer is the National Insurance Administration. However, special consideration can be made for chronic rare diseases (i.e. prevalence < 1/10,000) after individual application for reimbursement.

Other therapies for rare diseases

No information reported.

Orphan devices

The National Insurance Act⁴⁶² (folketrygdloven) gives rights for the use of assistive devices (orphan and common) for daily life activities and work.

Specialised social services

There are no special rights or specialised social services in Norway: all citizens have the same rights. As a user of long-term, coordinated health and/or social services in Norway, you are entitled to an Individual Plan (IP). The right to an IP is not conditional on a particular diagnosis or age, and is mentioned in several Norwegian acts. One service provider (coordinator) has the overall responsibility for each person's IP. To succeed as a coordinator it is essential to establish and maintain a relationship with the user based on trust and respect. An IP contains an outline of your objectives, your resources and the services you require. As a user you have the right to participate throughout the planning process.

National competence services (Centres of Expertise) offer residential training courses for patients, families and professionals. The courses include lectures, group discussions, consultations and joint activities. These courses are free of charge for patients and their families. Staff from the centres also visits people in their home environment, pass on information and hold guidance meetings, as well as making contributions to courses, conferences and seminars. Collaboration with local health services and staff ensures that people with

⁴⁶² <http://www.lovdatab.no/all/hl-19970228-019.html>

a rare disorder and their families receive treatment, care and services appropriate to their needs within their local community.

Frambu⁴⁶³ was established in 1954, with services to patients with polio, cerebral palsy, epilepsy etc., and offered services to 41 different rare diseases in 1991 : it now offers services for over 100 diseases to children, adolescents and adults. Frambu offers summer camps for four groups of around 50 children and adolescents each year, offering a chance to meet others in the peer's situation and build a network of friends and contacts. The centres of expertise for rare diseases provide these types of social services, which are meant to supplement generally available programmes.

2.5. SWITZERLAND

Definition of a rare disease

The Therapeutic Products Act (TPA) adopted the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals and this applies for the simplified authorisation of orphan medicinal products. Stakeholders in Switzerland accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategies for rare diseases and related actions

There is still no national concerted plan or strategy for rare diseases in Switzerland.

With the aim of filling this gap, on 16 December 2010, Ruth Humbel, member of the Health Commission in the Parliament submitted to the National Council a postulate for "*a national strategy for improving the health situation of people with rare diseases*". The National Council followed the recommendation of the Federal Council and accepted the claim in March 2011. The Federal Council has consequently assigned the Federal Office of Public Health the task of submitting a proposal. An alliance⁴⁶⁴ encompassing patient organisations, the Swiss Medical Association, university hospitals, the rare disease informational portal Orphanet-Switzerland and representatives from the pharmaceutical industry, then joined forces in August 2011 to promote a national strategy for rare diseases in Switzerland. Chaired by National Councillor Ruth Humbel, this newly-formed community of interest for rare diseases (*IG rare diseases*) is actively engaged in advocating the development of a national action plan for the country's rare disease patients. In September 2012, National Councillor Guy Parmelin requested information concerning the state of advancement of the national strategy for rare diseases. The answer of the Federal Council included the information that a formal meeting between the IG and the Federal Office of Public Health took place on 4 June 2012 to define the expectations and priorities for the development of a national plan. Issues such as financing diagnostic tests and defining the criteria for centres of expertise have been broached. A report on the advancement of the elaboration is due in Spring 2013 so as to determine the next steps in collaboration with the Swiss Academy of medical Sciences.

The Federal Office of Public Health is working on a project that will facilitate the reimbursement of rare disease medicinal products. A round table meeting held on 23 September 2011 gave health professionals, representatives of the biopharmaceutical industry, health insurances, patient organisations and local government representatives the opportunity to exchange views. Amongst the topics broached were strategies for reimbursing products and evaluating their benefits, as well as ways to improve diagnosis, for which the French model of identifying and creating networks of expertise was evoked. Finally, the issue of negotiating prices for rare disease treatments was discussed, as well as the necessity for clinicians and researchers to collaborate to enhance the understanding of rare disease treatments. A second round table was held in early 2012. The project should then be open for consultation later in 2012.

The Swiss Conference of the Cantonal Ministers of Public Health (GDK/CDS) also supports the publication of a manual for the employees of the information and counselling centres for prenatal testing and coordinates the offer of highly specialised medicine in Switzerland, including rare disease patients. The only specific project for rare diseases supported by the GDK/CDS is Orphanet Switzerland.

⁴⁶³ <http://www.frambu.no/>

⁴⁶⁴ http://www.orphanet.ch/PDF/MEDIENMITTEILUNG_Gruendung_IG_Seltene_Krankheiten_f_def.pdf

Centres of expertise

Several specialised care centres have been established as centres of reference by reputation, usually in University Hospitals. In addition to this, the Inter-Cantonal Agreement on Highly Specialised Medical Services (IAHSMS) coordinated by the GDK/CDS came into effect in 2009 the purpose of which is that *“the cantons shall agree, in the interests of a needs-based, high-quality and economical health care system, to ensure coordination in relation to the centralisation of highly specialised medical services. This applies to those medical fields and services that are characterised by their rarity, by their high potential for innovation, by high personnel or technical costs or by complex treatment procedures. For categorisation as a highly specialised medical service, at least three of the aforementioned criteria must be met, whereby rarity must always apply”*. The appointed centres can be consequently considered as official reference centres of expertise⁴⁶⁵. In 2011, several centres have been officially appointed in the fields of metabolic diseases, retinoblastoma, primary immunodeficiency in children, surgery of the liver and biliary tract in children, rare medullar tumours, surgery of epilepsy and neurosurgery of complex vascular anomalies of the central nervous system. In 2012, no new centres have been officially appointed, however, the procedure is still ongoing.

Registries

There are a number of registries for specific rare diseases in Switzerland. Switzerland contributes to the following European registries: AIR, CAPS, E-IMD, TREAT-NMD, EUROCARE-CF and EUROCAT.

Neonatal screening policy

A newborn screening programme covering all of Switzerland is in place and includes screening for phenylketonuria, congenital hypothyroidism, galactosaemia, congenital adrenal hypoplasia, biotinidase deficiency, and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. The request to implement the neonatal screening for cystic fibrosis, initiated by the Swiss Cystic Fibrosis Task Force, was approved from the Federal Office of Public Health in December 2010 and a 2-year-pilot project started in January 2011, with screening to be introduced in 2013.

Genetic testing

The medical genetics speciality exists for laboratory directors (FAMH) and for medical doctors (FMH) and several specialised care and/or testing centres have been established as centres of reference by reputation, usually in University Hospitals. Genetic testing laboratories require formal authorisation⁴⁶⁶ to practice from the government; more than 60 public and private laboratories provide genetic testing, although not all tests are reimbursed. Since 2011, interlaboratory comparisons (EQA or other) must be performed at least once per year for every analysis proposed by genetic testing laboratories. Genetic counselling is formally required and is usually provided by doctors specialised in medical genetics or by referring doctors.

The efforts of genetic health professionals led to the approval on 2 December 2010 by the Federal Department of Home Affairs of the introduction (as of 1 April 2011) of an orphan disease regulation for the reimbursement of genetic laboratory testing of rare genetic diseases by the compulsory health insurance even if this test did *not* appear in previous list of approved tests or if the test is carried out abroad. An individual application for reimbursement is required and has to be submitted to the health insurance medical examiner (HIME) responsible.

Diagnostic tests are registered as available in Switzerland for 371 genes and an estimated 436 diseases in the Orphanet database⁴⁶⁷; this information, however, is not yet complete and does not cover all of Switzerland.

National alliances of patient organisations

Since 2004, Orphanet Switzerland has identified about one hundred rare disease patient organisations, some of them being related to international networks. Since 2009, the “strategic” position of Orphanet Switzerland with regards to contacts with patient organisations, has actively contributed to the creation of an Alliance of Rare Diseases in Switzerland, facing the challenges of uniting patients from four different linguistic areas. ProRaris, the Swiss Rare Disease Patient Alliance, was founded on 26 June 2010 representing 42 patient organisations.

In 2011, ProRaris⁴⁶⁸, as a newly founded Alliance, put all its efforts in the increasing of awareness of rare diseases in Switzerland. In the framework of the 4th International Rare Disease Day, ProRaris organised

⁴⁶⁵ <http://www.gdk-cds.ch/index.php?id=903&L=1>

⁴⁶⁶ Federal Act on Human Genetic Testing (HGTA) of 8 October 2004, <http://www.admin.ch/ch/e/rs/8/810.12.en.pdf>

⁴⁶⁷ Information extracted from the Orphanet database (December 2012).

⁴⁶⁸ www.prorarais.ch

the first conference on rare diseases in Switzerland addressing the main topic “*Inequal access to health care*” with the lack of coverage by health insurances of genetic testing and orphan medicinal products

In addition to this major event, large media coverage has been achieved including a special television documentary on rare diseases and on the non-reimbursement for orphan products deemed too expensive (cf. Federal Court decision of 23 November 2010). The TV program⁴⁶⁹ was followed by a live debate on rationing health costs with, among others, the participation of the director of the Federal Office of Public Health.

At the end of August 2012 ProRaris submitted a case study on the unequal treatment of the reimbursement of drugs for patients with rare diseases among various insurance companies in different cantons to the director of the Federal Office of Public Health, Mr. Pascal Strupler. In his answer he announced a close monitoring of the interpretation of articles 71 a and b of the ordinance on health insurance (Krankenversicherungsverordnung) on which the decisions of the insurance companies are based until the end of 2013.

As a patient representative, ProRaris is part of the “Community of Interest for rare diseases”, founded in August 2011, and is strongly implied in political advocacy for the elaboration of a national plan for rare diseases.

Within the framework of the new project supported by the European Commission to support rare disease national plans, the proposal of ProRaris to organise, by 2013, a EUROPLAN conference in Switzerland with all stakeholders, which will be supported by EURORDIS, was selected.

Sources of information on rare diseases and national help lines

Orphanet activity in Switzerland

Since 2001 there is a dedicated Orphanet team in Switzerland, currently hosted by the Genetics and Laboratory Medicine Department of the University Hospital of Geneva. This team is composed of a country coordinator and, since 2011 of 2 information scientists (1 full time position and 1 part time position). Orphanet Switzerland has a close collaboration with the Health On The Net foundation (HON) for the management of the online forms. The team is in charge of identifying sources of information, collecting and updating data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) at national level for entry into the Orphanet database. In 2011 the team launched the Orphanet Switzerland national website⁴⁷⁰ and contributes to the dissemination of information regarding the Orphanet database tool and national initiatives in the field of rare diseases (publications, media coverage, Orphanews, conferences, booth at annual congresses of learned societies, etc.). The website is currently only available in French. Additional resources are necessary to translate the content in German and Italian.

As a collaborating partner of the Orphanet Joint Action, Orphanet Switzerland is not entitled to the EU funding and must ensure its funding at national level. In 2011, the Swiss Conference of the Cantonal Ministers of Public Health (GDK/CDS) guaranteed a global budget for 2011 and 2012 for Orphanet.

Official information centre for rare diseases

There is no official information centre for rare diseases, however Orphanet is the reference portal for information on rare diseases and orphan medicinal products in Switzerland.

Help line

There is currently no help line available for rare diseases in Switzerland. A joint venture between the University Hospital of Lausanne (CHUV) and the University Hospital of Geneva (HUG) with the support of Orphanet Switzerland was initiated in 2012 in order to create a regional portal on rare diseases and to establish a helpline. The services are planned to be available in 2013.

Other sources of information on rare diseases

The GDK/CDS supports the establishment of cantonal information and counselling centres for prenatal testing and the HGTA requires non directive genetic counselling before and after genetic testing. However, the existence of four national languages complicates the organisation of collective national projects. Orphanet Switzerland is currently the only rare disease project supported financially by the GDK/CDS.

The Federal Office of Public health publishes the list of the laboratories with an authorisation to execute genetic tests.⁴⁷¹

⁴⁶⁹ « Too expensive: you die ! »: <http://www.tsr.ch/emissions/36-9/3264987-trop-cher-tu-meurs.html>

⁴⁷⁰ <http://www.orpha-net.ch/?lng=FR>

⁴⁷¹ <http://www.bag.admin.ch/themen/medizin/00683/02724/03677/index.html?lang=de>

Good practice guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

National rare disease events in 2012

ProRaris organised events for Rare Disease Day, including an event with 350 participants from all stakeholder groups to learn about, discuss and share about the rare disease public health issue. The event was supported by the main University Hospitals (Geneva, Lausanne, Zurich and Bern), the children's hospitals of Zurich and Basel, Orphanet Switzerland, the BNP Paribas foundation and Gebert Rűf Stiftung. The event included the participation of Mr Pierre-Yves Maillard, President of the Conference of Cantonal Health Ministers and the cantonal Minister of Health of the Canton de Vaud, and Mr Pascal Strupler, the Director of the Federal Office of Public Health. Mr. Strupler announced the elaboration of a National Plan for Rare Diseases.

The 25th edition of the Swiss Telethon was held on 6-7 December 2012 in Lausanne⁴⁷².

Hosted rare disease events in 2012

A number of rare disease events were hosted by Switzerland in 2012 and announced in *OrphaNews Europe*: RE(ACT) Congress 2012 - International Congress on Research of Rare and Orphan Disease (Basel, 29 February 2012), 3rd Annual World Orphan Drug Congress (Geneva, 29-30 November 2012), Autoinflammation 2013: 7th International Congress of the International Society of Systemic Auto-Inflammatory Diseases (Lausanne, 22- 26 May 2013), International Congress on Research of Rare and Orphan Diseases (Basel, 29 February - 2 March 2012).

Research activities and E-Rare partnership

National research activities

Although there is no specific national budget for rare disease research, the Telethon Suisse raises funds for rare diseases, specifically for neuromuscular disorders. Moreover, many projects on rare diseases are supported by the Swiss National Science Foundation and a few public foundations (i.e. the Gebert Rűf Foundation and the BLACKSWAN Foundation). A new clinical research priority program of the University of Zurich - radiz - Rare Disease Initiative Zurich – was started in the fall of 2012. Radiz is funding translational research projects and supporting and training young clinicians and researchers with the aim to increase awareness for rare diseases and stimulate interdisciplinary collaborations.

The *Gebert Rűf Foundation*⁴⁷³, a Swiss grant programme specifically for rare diseases, announced its fourth call for projects in 2012. The independent foundation is committing CHF2 million (€1.66 million) per year to researchers based at Swiss universities, university hospitals, federal institutes of technology and universities of applied sciences. The Rare Diseases – New Approaches grant programme, which launched in 2009, is established as a five-year area of activity. The initiative aims at developing and implementing innovative technologies or approaches in the diagnosis and treatment of rare diseases. The first two calls in 2009 and 2010 selected ten finalists from 106 applications. Another call followed in 2011. In 2012, the chosen topics were: Molecular Basis of *Pseudomonas Aeruginosa* Persistence during Chronic Infections of Cystic Fibrosis Airways; Transient Neonatal Diabetes and ZFP57 as a Paradigm for the Exporation of Imprinting Disorders; Inducing Immunological Tolerance to Galsulfate as an Example in Enzyme Replacement Therapies; Uromodulin-associated Kidney Diseases; Optogenic Vision Restoration and Neuroprotection in Retinitis Pigmentosa.

The knowledge gained should lead to a better understanding of the genetic, molecular and biochemical processes underlying these diseases and pave the way towards new forms of treatment or diagnostics. A further aim is to improve the transfer of basic research findings into clinical practice. The focus must be on innovation, feasibility and effectiveness, while attaining high scientific and technological standards.

The *BLACKSWAN Foundation*⁶ is active since 2009 and supports advanced research into rare diseases in order to complement the chronic lack of public and private funds in this area. The principal goals are to promote and fund therapeutic application of new scientific protocols in order to find effective treatments and to increase public understanding and awareness of rare diseases.

⁴⁷² <http://www.telethon.ch/>

⁴⁷³ <http://www.grstiftung.ch/en.html>

⁶ <http://www.blackswanfoundation.ch/>

Participation in European research projects

Switzerland participates or has participated in European rare disease research projects including: AAVEYE, ANTIMAL, AUTOROME, BIOMALPAR, CELL-PID, CLINIGENE, CSI-LTB, CSI-LTB, DARTRIX, E-IMD EMVDA, EURADRENAL, EURO-LAMINOPATHIES, EUGINDAT, EURAPS, ESPOIR, EURENOMICS, EUREGENE, EUROBONET, EUROAGENTEST 1 AND 2, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EVI-GENORET, GAPVAR, GENESKIN, GEN2PHEN, HDLOMICS, HUMALAB, FIGHTHLH, INTEREALL, IMMUNOPRION, LEISHMED, LYMPHANGIOGENOMICS, MYELINET, MILD-TB, MPCM, MYORES, NEUROPRION, NANOTRYP, NOVSEC-TB, NM4TB, PEMPHIGUS, PULMOTENSION, RD-CONNECT, TRYPOBASE, THERAPEUSKIN, and SIOPEN-R-NET.

E-Rare

Switzerland is not currently a member of the E-Rare project although the BLACKSWAN Foundation is an active collaborator of the network.

IRDIRC

Swiss funding agencies have not yet committed funding to the International Rare Diseases Research Consortium (IRDIRC).

Orphan medicinal products

The Swiss Orphan Drug Regulation was introduced in 2006: this regulation stipulates that orphan medicinal product status applies to products treating diseases affecting no more than 1 in 2000 persons. The availability of orphan medicinal products has been improved since 2006 thanks to the simplified authorisation procedures and the recognition of the orphan medicinal product status for any drug for which this status has been granted in a country with a comparable drugs authority.

Orphan medicinal product committee

No specific activity reported.

Orphan medicinal product incentives

Companies acquiring orphan medicinal product designation for their products are allowed tax exemption for certain administrative taxes but are not however allowed market exclusivity.

Orphan medicinal product market availability situation

More than 100 medicinal products for rare diseases with EU market authorisation are marketed in Switzerland⁸.

Orphan medicinal product pricing policy

Compared to European Member States the pricing and reimbursement procedure in Switzerland is considered relatively quick and is speeded up when drugs target unmet medical needs or show high therapeutic benefit⁴⁷⁴.

Orphan medicinal product reimbursement policy

On 23 November 2010 the Federal Supreme Court decided that a health insurer was not obliged to reimburse the treatment costs (500'000 Swiss Francs per year) of Myozyme® for a patient with Pompe Disease, on the grounds that the therapy costs are not proportionate to the expected benefits for this specific patient. Based on this case, the Federal Court of Justice decided to fix limits for reimbursements, and although regretting the risk of unfairness, admits that rationing must be introduced. A limit of 100,000 Swiss Francs (€83'000) per year per patient has been proposed.

As of 2 February 2011 the Federal Council put two new articles of the Federal Ordinance on the Health Insurance into force stipulating that the off label use of drugs and the treatment with drugs not listed on the list of the reimbursed drugs (Spezialitätenliste) is admitted in case of life-threatening diseases if an important therapeutic benefit is expected from the treatment and if there is no reimbursed alternative. The Ordinance gives the insurers the freedom to decide about the maximum amount to be reimbursed.

⁷ Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p120

⁸ <http://www.swissmedic.ch/daten/00081/index.html?lang=de>

Other initiatives to improve access to orphan medicinal products

No specific activity reported.

Other therapies for rare diseases

Orphan devices

No specific activity reported.

Specialised social services

No specific activity reported.

2.6. TURKEY

Definition of a rare disease

According to the National Draft Guideline for Orphan Medicines, the prevalence limit for the definition of a rare disease will be within the EU-defined limit of no more than 5 in 10'000 individuals. The Ministry of Health accepts pricing of human medicinal products to be considered under the 'orphan' approach when such a product is indicated for the treatment of diseases for which the aetiology is not clearly defined and those which affect no more than 1 in 100'000 individuals⁴⁷⁵.

National plan/strategies for rare diseases and related actions

There is currently no national plan or strategy for rare diseases in Turkey: rare diseases are currently funded within the general health system budget⁴⁷⁶.

In 2010, the Turkish Ministry of Health considered collaboration with Orphanet Turkey in specific projects for the establishment of a National Plan for Rare Diseases and a number of meetings have been organised amongst professionals in Turkey in the context of the Europlan project of which Turkey is a collaborating partner. The recognition of a national plan is mandatory for assigning priority actions for rare diseases. Under the "National Health Transformation Programme" the Ministry of Health has suggested developments in medicinal product use, medical and social care, surveillance and other relevant actions⁴⁷⁷.

The 1st National Rare Disease Symposium took place on 27 November 2011 in Istanbul. Organised by the Orphanet Turkey team, this event brought together representatives from the Turkish Ministry of Health, Social Security authorities, patient organisations, scientists and industry. The symposium covered 3 main topics: rare disease and orphan medicinal products organisations and databases in EU; International and European Union and legislation on rare diseases and orphan medicinal products, and the current situation in Turkey; and problems and difficulties in the treatment and management of rare diseases in Turkey - how to overcome these obstacles. Participants discussed the current legislation at EU level in the field as well as the current situation in other countries such as Italy, France and Bulgaria. A second symposium is planned for 2012 is to discuss the areas to be considered in the scope of a national plan for rare diseases.

Centres of expertise

Though no centres of expertise for rare diseases currently exist, university hospitals and research centres are active in diagnosis and management of rare diseases, including centres at Hacettepe University Ankara) for metabolic and neuromuscular diseases, Istanbul University for neuromuscular diseases and Gazi University (Ankara) for metabolic diseases with the necessary infrastructure for specialised care (i.e. inpatient beds and outpatients clinics, pathology services, genetic counselling units, genetic testing facilities for post and prenatal diagnosis, biochemistry, physical therapy units, etc). These centres can accept referral patients from other

⁴⁷⁵ Press release regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

⁴⁷⁶ Notification regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

⁴⁷⁷ Turkey Health Transformation Program

(<http://www.saglik.gov.tr/EN/BelgeGoster.aspx?17A16AE30572D313AAF6AA849816B2EF1DACD7356F6C2568>)

<http://www.orpha.net/actor/EuropaNews/2009/doc/TurkHealthPolicy.pdf>

centres/cities and state hospitals and are therefore described as 'reference centres'. For these centres, the Ministry of Health and the social security system covers the invoices of non-private patients.

Turkey is planning to establish national networks for the prevention, surveillance, diagnosis and treatment of rare diseases. Projects to establish national centres of reference for rare diseases are expected. These centres will be part of the overall planning of healthcare in the country. The Ministry of Health and the different regional healthcare authorities will have to coordinate their approach and harmonise regional network activities.

Registries

In order to identify the rare diseases currently prevalent in Turkey, there is a significant need to complete a comprehensive epidemiological survey at national level: this is currently being developed by stakeholders. Within the IT infrastructure of Hacettepe Hospitals a new registry program including clinical and laboratory findings has been established for paediatric rare metabolic diseases. This registry is financed by Hacettepe Hospital and METVAK (Metabolic Diseases Foundation)

Turkey participates in the European registries EIMD, SCNIR, TREAT-NMD and EUROCARE CF.

Neonatal screening policy

The Ministry of Health is responsible for neonatal screening of phenylketonuria and congenital hyperthyroidism since 2007 and bitonidase deficiency since 2009. Data in 2011 shows that over 95% of the population is covered by these screening policies. Neonatal screening is coordinated by the Newborn Screening Coordination Centre based at the Refik Saydam Disease Prevention and Control Centre in Ankara. A free national screening and counselling program for thalassemia is also available through Thalassemia Counselling Centres organised by Turkish Ministry of Health.

Genetic testing

Genetic testing is carried out mainly at University laboratories. There are no national guidelines concerning genetic testing, but two information documents have been prepared by Hacettepe Medical School on ethical principles of genetic testing and counselling through the National Commission for UNESCO Bioethics Committee web site (in Turkish). Tests are reimbursed through the Social Security System and private insurance schemes. Testing abroad is possible.

Diagnostic tests are registered as available in Turkey for 111 genes and an estimated 164 diseases in the Orphanet database⁴⁷⁸.

National alliances of patient organisations and patient representations

There is currently no national alliance of rare disease patient organisations in Turkey, although there are a number of disease-specific patient organisations covering some rare diseases (i.e. cystic fibrosis, phenylketonuria and neuromuscular diseases). Some private foundations (such as the Foundation for Metabolic Disorders – METVAK) are active in counselling, creating public awareness and networking for patients and families.

Sources of information on rare diseases and national help lines

Orphanet activity in Turkey

There is no official, rare disease specific information centre on rare diseases in Turkey other than Orphanet. Since 2006 there is a dedicated Orphanet team for Turkey currently hosted by the Istanbul University Experimental Medical Research Institute Department of Genetics. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also maintains the national Orphanet Turkey website⁴⁷⁹ in the Turkish language. The team organised the 6th Eastern European Rare Disease Conference in Istanbul on 24-26 November 2011 and the 1st National Rare Disease Symposium in Istanbul on 27 November 2011: a second National Symposium is planned to take place in November, 2013.

Official information centre for rare diseases

There is currently no official information centre for rare diseases in Turkey, although information is provided by the Ministry of Health's Mother and Child Health Directorate in Ankara.

⁴⁷⁸ Information extracted from the Orphanet database (December 2012).

⁴⁷⁹ <http://www.orpha.net/national/TR-TR/index/orphanet-t%C3%BCrkiye/>

Help line

There is currently no official help line for rare diseases in Turkey.

Other sources of information on rare diseases

No specific activity reported.

Good practice guidelines

Treatment guidelines have been issued by the Ministry of Health for the following rare diseases: Gaucher type I and III; LSD type I, II and VI; Fabry; Niemann Pick; Pompe; and Wolman diseases.

Training and education initiatives

A bylaw has been accepted for fellowship training program paediatric metabolic diseases.

National rare disease events in 2012

Some rare diseases have an annual designated day (e.g. phenylketonuria day, 1 June) to raise awareness of these diseases.

Hosted rare disease events in 2012

No specific reported activities.

Research activities and E-Rare partnership

National research activities

TUBITAK (The Scientific and Technological Research Council of Turkey) has in the past supported research on rare diseases in Turkey.

Participation in European research projects

Turkish teams participate/participated, in the following European Reference Networks for rare diseases: Dyscerne, TAG and EN-RBD. Turkish teams participate/participated, in European rare disease research projects including: CELL-PID, CRANIRARE, CRANIRARE-2, EDEN, EURENOMICS, ELA2-CN, EMINA, EURO-CGD, EUROSCAR, NEUTRONET and PODONET.

E-Rare

Turkey, represented by TÜBİTAK, has been a member of the E-Rare and E-Rare-2 projects. TÜBİTAK participated in all Joint Transnational Calls (JTC) of the E-Rare-1 and E-Rare-2 projects. In the 1st Joint Transnational Call, Turkey was represented in 2 of the 13 consortia/projects selected for funding of €700'000. In the 2nd Joint Transnational Call E-Rare, Turkey was represented in 4 of the 16 consortia/projects selected for funding, with a total of around €400,000 funding. In the 3rd Joint Transnational Call, TÜBİTAK supported 3 Turkish research teams within 13 selected consortia. Turkey also participated in the 4th Joint Transnational Call in 2012, however teams from Turkey are not involved in the selected consortia. The fifth E-Rare joint transnational call (JTC 2013) for funding multilateral research projects on rare diseases have been decided to open on December 7, 2013 by 17 European organisations including TÜBİTAK. Turkish funding commitment is 0,6 M€ for the fifth call, submission deadline for full proposals will be 29 May 2013.

IRDiRC

With a Memorandum of Understanding (MoU) documenting, the commitment of the indicated E-Rare group of funders, who agree on making every reasonable effort to fulfil the intents expressed in their participation in IRDiRC, has been signed between each Party including TÜBİTAK. EC responded positively to this demand that the group of E-Rare funders joins IRDiRC in 2012.

Orphan medicinal products

At the end of 2011, the Directorate General of Pharmaceuticals and Pharmacy (IEGM), attached to the Turkish Ministry of Health, transformed into the independent national competent authority, The Turkish Medicines and Medical Devices Agency (TİTCK). In Turkey, licencing applications for all human medicinal products are submitted, by accredited licence holders, to TİTCK, in line with the "Regulation on Licencing for Medicinal Products for Human Use".

In 2010, the Orphan Drug Study Group (ODSG) was formed from officers working at the Directorate-General of Pharmaceuticals and Pharmacy (IEGM), TİTCK from here on. The main purpose of ODSG was to

prepare the national Guideline for Orphan Medicines. In the course of activities, ODSG compiled information relating to orphan medicinal products and rare diseases in the European Union (EU), studied Regulations 141/2000/EC and 847/2000/EC, and developed a national approach for orphan medicinal product policies in Turkey. The National Draft Guideline for Orphan Medicines was formed in the first quarter of 2011. The Draft Guideline was open for consultation by the pharmaceutical sector, and responses received by the second half of 2011.

Orphan medicinal product committee

The Draft Guideline for Orphan Medicines includes the establishment of a “Scientific Commission for Orphan Medicines”.

Orphan medicinal product incentives

Data exclusivity is applied in terms to original products for which no generic registration application has been submitted in Turkey since 1 January 2005 among the original products which have been registered for the first time in one of the countries within the Customs Union Area after 1 January 2001, and original products which shall be registered for the first time in one of the countries within the Customs Union Area after 1 January 2005. The data exclusivity period consists of 6 years to commence as of the first registration date of these products in the Customs Union Area. With regard to those products which benefit from patent protection in Turkey, the implementation of the data exclusivity period of 6 years is limited to this patent period⁴⁸⁰.

The Draft Guideline for Orphan Medicines will be the first legislative document which to introduce incentives for orphan medicines in Turkey.

Orphan medicinal product market availability situation

At present, the Turkish Ministry of Health (MOH) has not yet developed a national policy with reference to “rare diseases” and “orphan medicinal products”, as commonly defined inside the European Union (EU). Therefore, patients suffering from known rare diseases in Turkey access treatment with nationally licenced or non-licenced human medicinal products that have been granted marketing authorisation by other competent authorities under “orphan designation” and/or indicated for the treatment of specific rare diseases.

In 2012, 50 (74%) of the 68 designated and centrally authorised medicines under the EU orphan medicinal products legislation are accessible in Turkey⁴⁸¹. Of these orphan medicinal products, 21 are licenced in Turkey and 29 are procured by pre-licencing procedures. EU orphan medicinal products in Turkey are illustrated below.

Around half of the EU authorised orphan medicinal products accessible in Turkey are oncology-haematology products whereas nearly one quarter is gastroenterology-metabolism products, coming in first and second place, respectively. Oncology-haematology and gastroenterology-metabolism products also dominate the list of EU-authorised orphan medicinal products procured through pre-licencing procedures in Turkey.

Orphan medicinal product pricing policy

Normally, all drugs in Turkey are subject to a reference pricing policy. However, orphan medicinal products are exempted from this. Orphan products are priced up to the reference price laid down in official documents of the products where these products were imported and manufactured in its country of origin. Price of these products shall be revised making calculation on amounts of sales price every year. The Ministry of Health accepts pricing of human medicinal products to be considered under the ‘orphan’ approach when such a product is indicated for the treatment of diseases for which the aetiology is not clearly defined and those which affect no more than 1 in 100’000 individuals⁴⁸².

Orphan medicinal product reimbursement policy

All orphan medicinal products entering the market are 100% reimbursed.

Other initiatives to improve access to orphan medicinal products

⁴⁸⁰ Regulation on Licensing of Medicinal Products for Human Use

<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=226>

⁴⁸¹ Source: 6th Eastern European Conference for Rare Diseases and Orphan Drugs: Rare Diseases Policy Development in Eastern European Countries, 26 November 2011, Istanbul.

⁴⁸² Press release regarding the Pricing of Medicinal Products for Human Use

<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>

Orphan medicinal products are procured in Turkey by TITCK through 3 means. A medicine may be:

1. Licenced and already on the market for purchase;
2. Currently non-licenced in Turkey, however procured on grounds that it is approved in USA or the EU, or on a case-by-case basis in return for prescription ratification if its efficacy and safety is proven and a clinical trial protocol is running;
3. Approved under the scope of the compassionate use programme, to be clinically administered to patients.

Orphan devices

No specific activity reported.

Other therapies for rare diseases

No specific activity reported.

Specialised social services

Some therapeutic recreational programmes and services aimed at the integration of patients in daily life are provided by patient organisations and private foundations with the aid of private donations. Disability benefits can be obtained from the government towards special education classes.

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⁴⁸³ The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

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Co-funded by the



Co-funded by
the Health Programme
of the European Union