

**2012 REPORT ON THE STATE OF THE ART
OF RARE DISEASE ACTIVITIES IN EUROPE
OF THE
EUROPEAN UNION COMMITTEE OF EXPERTS
ON RARE DISEASES**



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

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

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ACRONYMS

General

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

Pilot European Reference Networks

Dyscerne - European network of centres of expertise for dysmorphology
ECORN-CF - European centres of reference network for cystic fibrosis
Paediatric Hodgkin Lymphoma Network - Europe-wide organisation of quality controlled treatment
NEUROPED - European network of reference for rare paediatric neurological diseases
EUROHISTIONET - A reference network for Langerhans cell histiocytosis and associated syndrome in EU)
TAG - Together Against Genodermatoses – improving healthcare and social support for patients and families affected by severe genodermatoses
PAAIR - Patients' Association and Alpha-1 International Registry Network
EPNET - European Porphyria Network - providing better healthcare for patients and their families
EN-RBD -European Network of Rare Bleeding Disorders
CARE-NMD -Dissemination and Implementation of the Standards of Care for Duchenne Muscular Dystrophy in Europe project
ENERCA - European network for rare and congenital anaemia – Stage 3

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 2011. 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 either the European Commission, its Agencies or national health authorities.

The report is split into five parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2011

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

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 Rare Diseases Task Force and EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products, including the reports of the national conferences organised in the context of the EUROPLAN project. 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 period 2007-2011 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

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>

the 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) and the 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. The methodology for the production of these previous reports is outlined in their respective introductions.

- **Reports of the EUCERD meetings**

The reports of 2011 meetings of the EUCERD (22-23 March 2011 and 24-25 October 2011) 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.

- **Rare Diseases Task Force publications**

Various reports of the RDTF have been used as sources of data to collect information on the state of affairs at both EU and Member State levels pre-2010, notably the reports of the RDTF WG on Standards of Care (concerning European Centres of Reference) produced between 2005-2008, including the RDTF Final Report – Overview of Current Centres of Reference on rare diseases in the EU – September 2005⁹ and the RDTF Meeting Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – September 2006¹⁰, as well as the RDTF Final Report – State of the Art and Future Directions – March 2008¹¹.

- **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 products¹² 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*)¹³. 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 has been provided for this year's edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding &*

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/Publication/RDTFECR2005.pdf>

¹⁰ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

¹¹ <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

¹² http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

¹³ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*
http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

*Market Access Issues, 2011 Edition*¹⁴ by Donald Macarthur: this report is referenced in footnotes when used. Information for the overview was also taken from the *Nature Reviews: Drug Discovery* article produced by the COMP/EMA Scientific Secretariat, *European regulation on orphan medicinal products: 10 years of experience and future perspectives*¹⁵.

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

The site of EURORDIS the European Organisation for Rare Diseases¹⁶, and the book *The Voice of 12,000 Patients: Experiences & Expectations of Rare Disease Patients on Diagnosis & Care in Europe* (produced using the results of the EURORDISCare¹⁷ surveys), were 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 2011 site¹⁸, maintained by EURORDIS, also provided information on events at Member State level¹⁹ concerning Rare Disease Day.

- **EUROPLAN national conferences final reports**

In the context of the EUROPLAN project (2008-2011), 15 national conferences were organised in collaboration with EURORDIS and national rare disease patient alliances in 2010-2011 in order to present the Council Recommendation on an action in the field of rare diseases, as well as discuss the Europlan recommendations/guidance document for the development of national plans and strategies in the field of rare diseases²⁰ and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports²¹ of these conferences were presented in a common format for ease of comparison. Information provided in these reports has helped update the information provided in this document. Readers of this report are encouraged to refer to these reports in addition to the present report as they provide further detail of the discussions of national approaches to rare disease policy.

- **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 and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links²² 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 report produced by the RDPlatform project²³, in particular the report *Rare diseases research, its determinants in Europe and the way forward*²⁴ was also used as a source for Part I.

- **OrphaNetWork News**

OrphaNetWork News is the internal newsletter of Orphanet, which communicates information to partners on Orphanet activities in each partner country. The data for this newsletter is collected through a systematic query of Orphanet Country Coordinators and Information Scientists in order to collect information concerning Orphanet country teams' involvement in rare disease meetings and

¹⁴ <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21532564>

¹⁶ <http://www.EURORDIS.org/secteur.php3>

¹⁷ http://www.EURORDIS.org/article.php3?id_article=1960

¹⁸ <http://www.rarediseaseday.org/>

¹⁹ <http://www.rarediseaseday.org/country/finder>

²⁰ http://www.euoplanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf

²¹ <http://www.EURORDIS.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports>

²² http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

²³ <http://www.rdplatform.org/>

²⁴ http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

conferences, as well as participation in Rare Disease Day events and partnerships. The review at national level yielded information for the events section for each Member State report.

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 EUCERD* and *2011 EUCERD 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 2010. 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 2011.

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 2012 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 2011 to be included in Part II. Final validation of Parts II and V were sent to the EUCERD Member State representatives for final validation, to the best of their knowledge, in May 2012.

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, Research and Innovation, Enterprise and Industry, and the EMA respectively: this process was carried out in March/April 2012 by the Scientific Secretariat of the EUCERD. The 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 2011 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 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.

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 2011 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.

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 to 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 2011.

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 EC 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) and Open Access Infrastructure for Research in Europe (OpenAire) initiatives.

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 2011.

Part V concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Norway and Switzerland as EFTA countries, Croatia and Turkey as candidates for EU membership, and Israel: Iceland has chosen to not contribute a country report this year. 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 expertise²⁵
- Pilot European Reference Networks
- Registries
- Neonatal screening policy
- Genetic testing²⁶
- 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 2011²⁷
- Hosted rare disease events in 2011²⁸
- Research activities (National research activities, Participation in European research projects²⁹, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability³⁰, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products)
- 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.

²⁵ The term “official centre of expertise” used in this report means officially designated via a (ministerial) procedure.

²⁶ This section contains data extracted in September 2011 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).

²⁷ As announced in OrphaNews Europe.

²⁸ As announced in OrphaNews Europe.

²⁹ Past and ongoing participation in DG Research and Innovation financed projects. Some countries have added information on additional European projects.

³⁰ 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.

1. EUROPEAN UNION MEMBER STATES

1.1. AUSTRIA

Definition of a rare disease

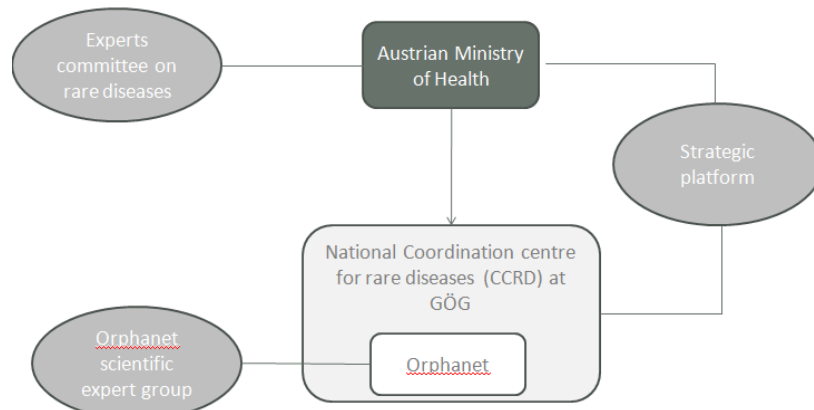
In 2010 there was still no official definition of rare diseases in Austria; on an informal basis, stakeholders in Austria accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 persons. In the national plan of action (still under development; 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 organisation 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 by 1 January 2011 at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG) and has a team of 1.4 full time equivalents and integrates part of the Austrian Orphanet team. Most members of the subcommittee for rare diseases 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 to the previous structure a strategic platform was set up, the is composed of Ministry of Health delegates, academic experts and payers (Austrian provinces and the Main association of the Austrian social security institutions),

Figure 1: Organisational Chart of the Austrian CCRD in 2011



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 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 2011, besides setting up its organisational structures and processes, were as follows:

- Acting as the the main driving force in drawing the national plan of action until end of 2013;
- Awareness raising among professionals / experts / doctors / patients on the topic of rare diseases;
- Active participation in the EU-funded project Orphanet as well as other European initiatives in this area (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);
- Information provision:
 - Establishment of Orphanet national scientific advisory board;
 - Establishment of national Orphanet website;
 - Updating of information on rare diseases in Austria ;
- Perform a large scale needs assessment survey regarding rare disease involving academics, stakeholders and – for the first time in Austria – patients and draft a report that is planned to be published in summer 2012;
- Drafting eligibility criteria for the establishment of Centres of Expertise based on EUCERD recommendations and discuss them with the Austrian stakeholders;
- Acting as the communication hub between actors in the field, focussing in the first years on health care professionals and other stakeholders and will contribute to ensuring that the unique challenges faced by people with rare diseases to meet are targeted;
- Acting as the focal point for European activities in the field of rare diseases, i.e. to keep track of developments and trying to draft a landscape of activities involving Austrian institutions.

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 “Spezialambulanz Genodermatosen” for Epidermolysis bullosa in Salzburg. The Austrian Ministry of Health supports the concept of such centres and has asked the CCRD to work on this topic.

It is therefore expected that future centres of expertise will be identified and suitable ones will be officially designated as soon as :

- a) the final criteria for European centres of expertise have been developed by the European Union Committee of Experts on Rare Diseases,
- b) these criteria have been adapted to meet national legal requirements, taking into account pre-existing structures of the Austrian health care system as will be reflected in the national plan of action for rare diseases,
- c) that either the necessary funds have been generated or, which is the preferred option, ways for a cost-neutral establishment of such CoE have been found, and
- d) the national plan has been implemented.

The nomination of centres of expertise and related expert clinics constitutes one of the actions in the national plan for rare diseases, covered by the strategic priority “Improving health care pathways”.

Pilot European Reference Networks

Austrian teams participate, or have participated, in the following European Reference Networks for rare diseases: EUROHISTIONET, NEUROPED (main partner), European network of paediatric Hodgkin's lymphoma, and PAAIR.

Registries

Currently, no nationwide, general, comprehensive registry for rare disease patients exists in Austria. Approximately 10-15 registries 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 additionally supported by corresponding patient support groups. Some of the

European registries Austrian teams participate in are EURO CARE CF, AIR, EIMD, EMSA-SG, EUROCAT 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 2011.

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 homepage³¹ 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 1994³² and last revised in 2005³³. 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

³¹ <http://www.meduniwien.ac.at/hp/neugeborenen-screening/>

³² http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/510_1994.pdf

³³ <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 sickness fund, even if the analysis is requested/recommended by a specialist for human genetics (in Tyrol, for instance, all genetic determinations that cost more than €1.000 need to be authorised by a sickness fund “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 109 genes and an estimated 172 diseases in the Orphanet database³⁴.

National alliances of patient organisations and patient representation

3 December 2011 was a milestone for patients suffering from rare diseases in Austria as on this date the umbrella organisation for patient organisations dealing with rare diseases was founded. This national “Allianz für seltene Erkrankungen” is called “Pro Rare Austria” and was founded by Dr. Riedl who is also spokesperson of DEBRA Austria, the Epidermolysis bullosa patient support group. As first broadly recognised activity the new Pro Rare team organised the Rare Disease Day 2012 in Vienna but also participated in a number of rare disease events (e.g. at the Mariazell follow-up Congress on Rare Diseases on 3-4. December 2011 hosted by the Medical University of Vienna).

Pro Rare Austria demands:

- Official recognition of defined rare diseases
- Public acknowledgment of the special status of patients suffering from rare diseases, namely
 - Exemption from any co-payments or cost-sharing for any treatment related to their rare disease
 - Unrestricted access to medicinal investigations, tests and diagnosis in Austria, and if not available nationally, within the EEA

³⁴ Information extracted from the Orphanet database in September 2011.

- Unrestricted access to all available therapies and medicines especially orphan drugs in Austria, and if not available nationally, within the EEA
- Austrian-wide uniform regulations with regards to long term care, care-support and childcare
- Improvement of medical care by establishment or designation of regional and/or national reference clinics/reference centres
- Promotion of scientific research aimed at developing therapies

Delegates of Pro Rare and a few other patient organisations were also invited to become member of the newly established Expert Committee for rare diseases (see Figure 1).

Apart from Pro Rare general alliances of patient organisations (both for rare and non-rare diseases) do exist on the province 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 also 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 their country for entry into the Orphanet database. The strategy behind this “two team approach” is to structurally integrate Orphanet (on a long run) into the Austrian health care system. Therefore, the teams are no rivals but cooperate very closely.

In 2011, the Orphanet-Austria³⁵ 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. In January 2011, the national Coordination Centre for Rare Diseases (Nationale Koordinationsstelle für Seltene Erkrankungen, NKSE) was established at the Austrian Health Institute Gesundheit Österreich³⁶ (as part – and first structural measure – of the national plan of action under development). NKSE is funded by the Austrian Ministry of Health (Bundesministerium für Gesundheit) and shall act in the mid-term 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 website³⁷ and provided information to health professionals, e.g. by presenting on rare disease specific congresses and events.

Help line

There is currently no official nation-wide national helpline for rare diseases in Austria. In April 2010, a more regional helpline was established 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

³⁵ <http://www.orpha.net/national/AT-DE/index/startseite/>

³⁶ <http://www.goeg.at/de/Bereich/Koordinationsstelle-NKSE.html>

³⁷ www.orpha.net/national/AT-DE/index/startseite

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)³⁸.

- A number of medical departments or patient registries also host websites with comprehensive and useful information on those rare diseases they are focusing on³⁹.
- In 2011 also rare disease specific information was provided on the official governmental health platform for Austria. Examples of information provided are excerpts regarding the patient, payer and stakeholder survey performed by the Austrian National Coordination Body for Rare Diseases (NKSE)⁴⁰ as well as information regarding the establishment of the NKSE⁴¹.

Good practice guidelines

No specific information reported.

Training and education initiatives

The Academy of the Epidermolysis Bullosa House 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 2011

A day dedicated to rare diseases was held on 26 February 2011 at the Paracelsus Medical University Salzburg to celebrate the 4th Rare Disease Day. Also on 26 February 2011, the “walk for rare diseases” took place in Vienna, again featuring more participants than in previous years.

On 2 and 3 December 2011, the Medical University of Vienna and the National Action Platform for Rare Diseases (NASE) held the Austrian Congress on Rare Diseases 2011 in Vienna. The conference was planned as a follow-up event from the 2010 congress in Mariazell and once again was attended by a large range of stakeholders to encourage discussion, to raise awareness and to look for solutions.

In addition to these events, the Second Regional Forum for Rare Diseases was held on 20-21 May 2011 in Innsbruck.

Hosted rare disease events in 2011

In addition to above mentioned events, a symposium pre-congress symposium to the International Congress on Prevention of Congenital Diseases, entitled Combating Rare Genetic Diseases - Clinics and Networking in Science, was held on 12 May 2011.

Rare diseases were also a topic at the 3rd International Congress for Quality Management in Villach that was held in the frame of the EU InterReg Project between Italy, Austria and Slovenia (Presentation: Management seltener Erkrankungen: Erfahrungen in Österreich - Entwicklungen in Österreich).

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

³⁸ 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>

³⁹ 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).

⁴⁰ www.gesundheit.gv.at/Portal.Node/ghp/public/content/aktuelles/seltene-erkrankungen-befragung.html

⁴¹ www.gesundheit.gv.at/Portal.Node/ghp/public/content/aktuelles/koordinationsstelle-seltene-erkrankungen.html

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: BNE, CLINIGENE, DIRECT, EDEN, EMSA-SG, EFACTS, EMINA, ENRAH, ENCE-PLAN, EURIPFNET, EUROTRAPS, EURO-IRON1, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROWILSON, GENEGRIFT, GENESKIN, GENOMIT, IMMOMEK, IntReALL, LEUKOTREAT, LYMPHANGIOGENOMICS, MYELINET, NEUTRONET, NEUROPRION, PERXISOMES, PNSEURONET, PROTHETS, PULMOTENSION, PWS, RARE-G, RHORCOD, RD-Connect⁴², RD PLATFORM, WHIPPLE’S DISEASE, SARS/FLU-VACCINE and TUB-GENCODEV. Austria is part of the SIOPEN-R-NET research network and networks resp/registries such as ERCUSYN, EUROCAT, IDR, PRINTO, SCNIR and RARECARE.⁴³

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)⁴⁴ 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-

IRDiRC

Austrian funding agencies are not currently a committed members of IRDiRC.

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)⁴⁵”.

Orphan medicinal product market availability situation

As soon as marketing authorisation is provided, orphan drugs 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 still improve availability.

In 2011, 51 of the 62 orphan drugs with existing EU marketing authorisation were available in Austria and were used at least once. For the remaining orphans no out-patient use was documented, but it is possible that they were used in-patient, i.e. during hospital stay. Only Plenadren is not marketed for sure in Austria. Regarding reimbursement status and the meaning of “boxes” please see the section below. It is important to note, however, that the label “no box” does not mean that patients have no access or that it is not publicly funded, it just means that it is not included in the Austrian out-patient positive list.

Table 1. Availability of authorised orphan drugs in Austria in 2011/2012

Active Ingredient	Brand name	Company	Outpatient reimbursement
Pegvisomant	Somavert	Pfizer	N
Clofarabin	Evoltra	Genzyme	N
Imatinib Mesilat	Glivec	Novartis Europharm	N
Mercaptopurin	Mercaptopurin Nova Labo	Nova Laboratories	n.a.

⁴² Positive evaluation but contract not yet concluded.

⁴³ Based on information provided by the national EU database team PROVISO.

⁴⁴ <http://www.fwf.ac.at/>

⁴⁵ *Inventory of Community and Member States’ incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p7).*

Histamin Dihydrochlorid	Ceplene	EpiCept GmbH	N
Arsentrioxid	Trisenox	Cell Therapeutics (UK)	N
Tafamidis	Vyndaquel	Pfizer	N
Aztreonamlysin	Cayston	Gilead	N
Tobramycin	TOBI Podhaler	Novartis Europharm	Y
Ofatumumab	Arzerra	GlaxoSmithKline	N
Nilotinib	Tasigna	Novartis	N
Dasatinib	Sprycel	Bristol-Myers Squibb	N
Rilonacept	Rilonacept Regeneron	Regeneron	n.a.
Ibuprofen	Pedea	Orphan Europe	N
Trabectedin	Yondelis	Pharma Mar S.A.	N
Deferasirox	Exjade	Novartis Europharm	N
Dexrazoxan	Savene	SpePharm	N
Icatibant	Firazyr	Jerini AG	Y
Betain	Cystadane	Orphan Europe	N
Carglumsäure	Carbaglu	Orphan Europe	N
Pirfenidon	Esbriet	InterMune	R
Romiplostim	Nplate	Amgen	Y
Eltrombopag	Revolade	GlaxoSmithKline	Y
Busulfan	Busilvex	Pierre Fabre	N
Thiotepa	Tepadina	Adienne S.r.l.	N
Amifampridin	Firdapse	Eusa Pharma SAS	n.a.
Sorafenib	Nexavar	Bayer HealthCare	N
Rufinamid	Inovelon	Eisai	N
Bosentan	Tracleer (Ftbl)	Actelion Registration	Y
Iloprost	Ventavis	Schering AG	Y
Sildenafil	Revatio (Ftbl)	Pfizer	Y
Ambrisentan	Volibris	GlaxoSmithKline	Y
Nelarabin	Atriance	GlaxoSmithKline	N
5-Aminolaevulinsäure	Gliolan	Medac	n.a.
Plerixafor	Mozobil	Genzyme	N
Miglustat	Zavesca	Actelion Registration	Y
Velaglucerase alfa	VPRIV (1 ST)	Shire	Y
Alglucosidase alfa	Myozyme	Genzyme Europe	N
Zinkacetat Dihydrat	Wilzin	Orphan Europe	N
Laronidase	Aldurazyme	Genzyme Europe	N
Idursulfase	Elaprase	Shire	N
Galsulfase	Naglayzme	BioMarin	n.a.
Lenalidomid	Revlimid	Celgene Corporation	N
Thalidomid	Thalidomide	Celgene Corporation	N
Azacitidin	Vidaza	Celgene Corporation	N
Stiripentol	Diacomit	Laboratoires Biocodex	n.a.
Hydrocortison	Plenadren	Duocort Pharma	Not marketed
Mitotan	Lysodren	Laboratoire HRA	Y
Temsirolimus	Torisel	Wyeth	N

Cladribin	Litak	Lipomed	N
Mifamurtid	Mepact	IDM Pharma	N
Levodopa/Carbidopa	Duodopa Gel	Abbot Products GmbH	N
Eculizumab	Soliris	Alexion Europe	N
Sapropterin	Kuvan	Merck Serono	Y
Coffeincitrat	Peyona	Chiesi Farmaceutici	N
Mecasermin	Increlex	Tercica	Y
Ziconotid	Prialt	Eisai Limited	N
Hydroxycarbamid	Siklos	Addmedica	n.a.
Porfimer Natrium	Photobarr	Axcan Pharma	n.a.
Everolimus	Votubia	Novartis Europharm	N
Anagrelid-Hydrochlorid	Xagrid	Shire	n.a.
Nitisinon	Orfadin	Swedish Orphan	n.a.

N = No box, R = Red box, Y = Yellow Box, n.a. = non information on use available

Source: Austrian PPI service 2012

Orphan medicinal product pricing policy

In case a marketing authorisation holder applies for reimbursement by the Austrian Social Insurance in case of out-patient treatment, i.e. inclusion in the positive list “Erstattungskodex”, 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 Association of Austrian Social Security Institutions after some negotiation with the company. The way of the application and the decision process is regulation by a specific regulation called VO-EKO in German.

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

If the orphan drug is not reimbursed its price may be determined by the manufacturer alone. Unauthorised orphan drugs may be imported on case-by-case decisions. The vast majority of orphan drugs are dispensed in hospitals

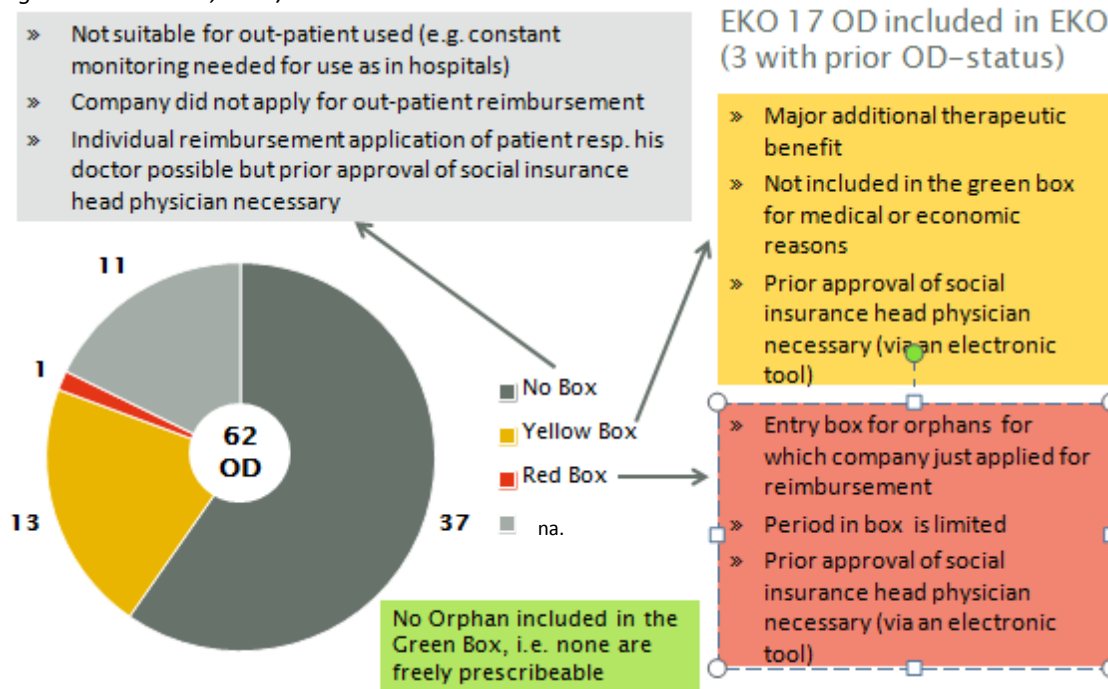
Orphan medicinal product reimbursement policy

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 reasonable⁴⁶. Contract physicians are entitled to prescribe all medicines included in the Austrian Reimbursement Code (EKO)⁴⁷ - 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. A reply is sent within 30 minutes latest. 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.

⁴⁶ Art. 133 ASVG 1955, regulating the extent of medical treatment [Art. 133 ASVG 1995; BGBl. No. 189/1955]

⁴⁷ Art. 31.3(12) ASVG, on the publication of the Reimbursement Code EKO (Art. 31.3(12))

Figure 2: Out-patient reimbursement status of all authorised orphan medicines with an active orphan designation in Austria, 2011/2012⁴⁸



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 “Elaprase”, 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 medicines not included in the EKO, the attending physician may still seek approval from the sickness fund (e.g. requesting administration of the orphan 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 orphans 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 provision of orphan drugs 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.

In 2011 public expenditure per prescription for orphan drugs amounted to around €2,700.- which is a small decrease compared to €2,771.- in 2010. Altogether the Austrian Social Insurance spent €85.3 million on orphan drugs in 2010, and €93.2 in 2011⁴⁹. In 2010 3.3% of all pharmaceutical expenditure was caused by orphan drugs where as expressed by number of prescriptions the share was only 0.03%.

⁴⁸ Source: CCRD 2012 based on EKO 1/2012 and Warenverzeichnis 1/2012.

⁴⁹ See table 2.

Table 2: Expenditure of Austrian Social Insurance for medicines and orphan drugs used out-patient, 2009 and 2010⁵⁰

Indicator	2009	2010
Expenditure		
Total PE by Social Insurance	2.575.279.455	2.595.067.053
Social Insurance Expenditure for Orphan Drugs*	74.600.543	85.296.165
OD share on Total PE	2,9 %	3,3 %
Medicines Prescriptions		
Total number of prescriptions	117.080.832	118.021.978
No. Of OD-prescriptions *	27.085	30.778
OD share on total number of prescriptions	0,02 %	0,03 %
Ø Cost per prescription		
All medicines	22,00	21,99
Orphan Drugs *	2.754,30	2.771,30

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.

Orphan devices

No specific information 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

After the implementation of the National Cancer Plan 2008-2010, 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 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:

⁵⁰ Note: All medicines expenses below the prescription fee (around € 5,-) are not included in these figures. Source: Austrian Social Insurance 2012 (Maschinelle Heilmittelabrechnung).

- 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 1⁵¹ 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 languages⁵². 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 new government is now in place which will analyse the propositions 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.

Concurrently, the Centres for Human Genetics (represented by the High Council for Anthropogenetics) have formulated suggestions for the development of a national health care structure for the management of patients with 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 foreseen for the development and the strengthening of these types of multidisciplinary centres of expertise. A group of experts is currently working to set up the criteria 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, i.e. they offer different types of tests and technologies, and patient and family counseling.

Pilot European Reference Networks

Belgian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, EPNET, EPI, ENERCA, EUROHISTIONET, NEUROPED, PAAIR, EN-RBD and TAG.

Registries

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 specific budget was foreseen in 2011 for the preparation of a conceptual note concerning the creation of a Central Registry of Rare Diseases. The conceptual note, approved by a group of stakeholders was accepted in December 2011 and a new budget was allocated for 2012-2013 to the Scientific Institute of Public Health.

Belgian teams also contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, EIMD, ENRAH, EUNEFRON and EURECHINOREG. Belgium contributes to the EUROPLAN project.

Neonatal screening policy

Neonatal screening in Belgium 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,

⁵¹ <http://www.kbs-frb.be/publication.aspx?id=271066&LangType=2060>

⁵² <http://www.kbs-frb.be/publication.aspx?id=288128&LangType=1033>

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 High Council for Anthropogenetics 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 proposal for the creation of a convention between the NIHDI and the genetic centres that will be launched in 2012.

Diagnostic tests are registered as available in Belgium for 355 genes and an estimated 376 diseases in the Orphanet database⁵³.

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 45 patient organisations for rare diseases in Belgium and is affiliated with EURORDIS. 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.

Sources of information on rare diseases and national help lines

Orphanet activities in Belgium

From 2001 onwards there was a dedicated Orphanet team in Belgium. At the beginning of 2011 the team was hosted by the Centre of Human Genetics at the Catholic University of Leuven. From April 2011 onwards, with the start of the Orphanet Joint Action, a team for Belgium has been designated at the Scientific Institute for Public Health 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 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 the Orphanet webpages 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

⁵³ Information extracted from the Orphanet database in September 2011.

gathered on the existing rare disease services and research activities in Belgium. Currently the validation procedure is being revised.

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. 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 their development 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 2011

On 22 February 2011 a symposium was organised by the Consultative Committee on Bioethics and the Fund for Rare Diseases and Orphan Drugs in collaboration with RaDiOrg.be on the theme of health care for rare diseases and its societal and ethical dimensions.

On 26 March 2011, RaDiOrg.be held their members meeting, which concentrated on the proposals made by the Fund for Rare Diseases and Orphan Drugs for a Belgian Plan for Rare Diseases. Particular focus was given to the discussion on the role of patient organisations in the plan, especially the role patients can play in giving feedback on their experiences of centres of expertise in Belgium.

Hosted rare disease events in 2011

On 28 February 2011 EURORDIS, in collaboration with DG Health and Consumers, organised a conference entitled 'The rare disease landscape in Europe: gaps in health care and social services' to mark Rare Disease Day 2011.

Amongst the rare disease events hosted in Belgium this year and announced in *OrphaNews Europe* were: the European Perspectives in Personalised Medicine (12-13 May 2011, Brussels, Belgium), the IPOPI EU-PID Forum (15 June 2011), 11th EUROCOT Symposium on Congenital Anomalies (17 June 2011, Antwerp), 18th Paediatric Rheumatology European Society Congress (PRES2011) (14-18 September 2011, Bruges), EPPOSI Advanced Innovation programming Day (20 October 2011, Brussels). The ESH Enerca Training Course on Haemoglobin disorders: Laboratory diagnosis and Clinical Management, in association with the Thalassaemia International Federation, was held from 1-2 April 2011 in Brussels.

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)⁵⁴ 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.

⁵⁴ www.frs-fnrs.be

Participation in European research projects

Belgian teams participate, or have participated, in the following a number of European research projects for rare diseases, including: ANTIMAL, CONTICANET, CHEARTED, ESDN, ENRAH, EURAMY, EUREGEN, EUROCARE-CF, EUROSCA, EVI-GENORET, FASTEST-TB, EUNEFRON, EURO-CDG, EUROAGENTEST, EUROGLYCANET, EURO-SCAR, GENESKIN, GEN2PHEN, GENOMIT, HUE-MAN, KALADRUG-R, LEISHMED, IMMUNOPRION, MITOTARGET, MYASTAID, NANOTRYP, NEOTIM, NEUROPRION, PEROXISOMES, PULMOTENSION, PWS, RATSTREAM, RD PLATFORM, SIOPEN-R-NET, STEM-HD, TRANSPOSMART, 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)⁵⁵ 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.

IRDiRC

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

Orphan medicinal products⁵⁶

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^{57,58} 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 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 following orphan medicinal products are available on the market in Belgium: Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Elaprased, Evoltra, Exjade, Firazyr, Gliolan, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Revatio, Revlimid, Savene, Soliris, Somavert, Sprycel, Siklos, Tasigna, Thelin, TOBI Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Yondelis, Zavesca.

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)⁵⁹. A last possibility for non-reimbursed pharmaceutical products is reimbursement by the Special

⁵⁵ www.fwo.be

⁵⁶ 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).

⁵⁷ <http://www.weesziekten.be/symposiumfr.htm>

⁵⁸ <http://www.maladiesrares.be/symposiumfr.htm>

⁵⁹ *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (p40).

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 budget⁶⁰.

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 hospitals⁶¹.

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"⁶².

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 indications⁶³. 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.

The list of orphan medicinal products reimbursed by the NIHDI⁶⁴ includes: Afinitor, Aldurazyme, Atriance, Benefix, Busilvex, Carbaglu, Cystadane, Diacomit, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Flolan, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tasigna, Thelin, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Xagrid, Xyrem, Yondelis, Zavesca⁶⁵.

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 2011, there were 28 colleges for 50 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 months⁶⁶ and can be renewed.

A study entitled "Policies for Orphan Diseases and Orphan Drugs"⁶⁷, 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.

⁶⁰ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp35-45).

⁶¹ Orphan Drugs in Europe : Pricing, reimbursement, Funding and Market Access Issues (2011 Edition), Donald Macarthur, (p 99).

⁶² Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p8).

⁶³ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p39).

⁶⁴ http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/OrphanCns.asp (updated 01/04/2010)

⁶⁵ Please note that for Afinitor, Sutent and Xyrem, the orphan designation was withdrawn.

⁶⁶ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp43-44).

⁶⁷ Link to the report: http://www.kce.fgov.be/index_en.aspx?SGREF=5211&CREF=13651

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*⁶⁸ 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. 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.

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;

⁶⁸http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=20482245

- 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 has been established by the Ministry of Health, and meets once a month to supervise the progress and implementation of the plan: the Council includes medical professionals, Ministry 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 towards genetic testing activities). The estimated budget does not envisage 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 Ministry of Health (defined by Ministerial Ordinance 34) and 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.

In addition to these measures, the First National Conference for Rare Diseases in Bulgaria (28 to 30 May 2010)⁶⁹, 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 consultation⁷⁰.

Centres of expertise

Currently, there is no official designation procedure for centres of expertise for rare diseases in Bulgaria. The national plan will carry out a feasibility study on the necessity, possibility and criteria for the creation of a centre of expertise for rare diseases. However, 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. The requirements and criteria for the designation of centres of expertise are under discussion: it is expected that these centres would be located within university hospitals. The envisaged network will include 5-6 centres at national level: the centres will be equally distributed geographically throughout the country and will deal with all rare diseases.

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

⁶⁹ <http://www.conf2010.raredis.org/>

⁷⁰ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Bulgarian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

“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.

Pilot European Reference Networks

Bulgaria participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne and Care-NMD.

Registries

Seven nation-wide epidemiological registries concerning rare diseases have been identified: the National Registry of Patients with Thalassaemia 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 and the the National Cancer Registry.

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 2011⁷¹.

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 published⁷². The Crohn Disease National Registry is already working and its first statistics⁷³ 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. A unique character of all BAPES-managed epidemiological registries for rare diseases is that they involve joint activities by all relevant stakeholders.

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

Bulgaria also contributes to the EUROCARE 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 Nr.26 2007 of the Bulgarian 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.

⁷¹ http://www.raredis.org/?page_id=2432&mel=4&smel=41&lang=en

⁷² http://www.raredis.org/?page_id=2447&mel=4&smel=44&lang=en

⁷³ http://www.raredis.org/?page_id=2454&mel=4&smel=43&lang=en

Genetic testing

Genetic tests for the diagnosis of rare disorders are provided mainly by the National Genetic Laboratory (NGL). This organisation 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.

Diagnostic tests are registered as available in Bulgaria for 34 genes and an estimated 40 diseases in the Orphanet database⁷⁴.

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

ICRDOD⁷⁵ is a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES⁷⁶) - 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.

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 March 2011 an updated review of the access to orphan medicinal products for rare diseases in Bulgaria⁷⁷: 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, 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.

A review of rare diseases patient registries in Bulgaria is currently under preparation.

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

⁷⁴ Information extracted from the Orphanet database in September 2011.

⁷⁵ <http://www.raredis.org/>

⁷⁶ http://www.raredis.org/?page_id=2147&mel=8&smel=81&lang=en

⁷⁷ http://raredis.org/pub/OD_Report_04042011_EN.pdf

“Rare Diseases & Orphan Drugs”, an online registry of rare diseases patients, an updated Rare Diseases Library in Bulgarian, as well as better interaction between the different users and ICRDOD team.

Since December 2010 ICRDOD publishes a newsletter⁷⁸ on a bi-monthly basis. It focuses recent advances and news, concerning all rare diseases stakeholders. 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).

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.

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.

Training and education initiatives

The first Eastern Europe Rare Diseases Summer School⁷⁹ designed for Russian health authorities and legislative institutions was held on 11-18 September 2011. It 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. Several rare diseases school initiatives are being planned for 2012.

Furthermore, BAPES organised for a second consecutive year in a row a two-day rare disease training seminar for medical students. 30 medical students had 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.

A training workshop for people with rare diseases was held on 1-7 May 2011 in Veliko Tarnovo.

National rare disease events in 2011

Every January, there is an annual meeting of the Consultants of the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD).

For the fourth consecutive year Rare Disease Day was marked in Bulgaria by various events organised by the National Alliance of People with Rare Diseases with the support of BAPES.

This year's event started on 12-13 February 2011 in Plovdiv with a training workshop “Psychological methods – way of self-help to improve quality of life of people with rare diseases and their families”. On 28 February 2011 a formal press-conference was held in Sofia. Rare disease stakeholders presented the newest achievements in this field across Europe and current problems in Bulgaria. The main focus of the Rare Disease Day in Bulgaria was the relation between patients and GPs. A series of training workshops on rare diseases for general practitioners was organised in Sofia, Plovdiv, Varna, Stara Zagora and Pleven. Leading medical experts presented the specifics of selected rare diseases as cystic fibrosis, pulmonary hypertension, epidermolysis

⁷⁸ http://www.raredis.org/?page_id=2311&mel=7&smel=71&lang=en

⁷⁹ http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf

bullosa, primary immunodeficiencies, thalassemia major, hereditary angioedema, Wilson disease, porphyrias, acromegaly. This initiative was a response to the requests of Bulgarian rare diseases patients at last year's Bulgarian EUROPLAN national conference. Parents of children with rare diseases particularly stressed the importance of GPs' awareness of rare diseases and the need for more efficient communication with them. The importance of Orphanet as an important source of quality information on rare diseases' field was outlined during this training workshops. GPs and even profile specialists were reminded that whenever they have a possible rare disease case they should feel free to seek some expert help and refer to validated information such as that of Orphanet. Medical students and patient associations organised a "teddy bear hospital" in Varna to help children overcome their fear of hospitals and doctors by playing games. The finale of the event was a charity rock concert on the main city square in Pleven (27 February 2011). Information was distributed in Bulgaria's major cities on 28 February.

The Second National Conference for Rare Diseases and Orphan Drugs was held on 9-11 September 2011⁸⁰ in Plovdiv. Topics⁸¹ included epidemiological registries for rare diseases, best practice guidelines for rare diseases management, health policy and legislation, access to orphan medicinal products in Bulgaria, the Bulgarian National Plan for Rare Diseases, European projects and programmes. The forum succeeded in creating a stage for a useful discussion of the current problems of rare diseases patients and medical professionals. A particular focus was the underperforming of the current National programme, which has not come yet to establish a national registry or reference centres. Just two years before the planned end of this plan, Bulgarian rare diseases stakeholders agreed that it is crucial to have a clear declaration of political willingness from the Ministry of Health for the implementation of the National plan, as well as an adequate funding for the foreseen activities, so the plan could reach its initial objectives. All the plan-identified measures should be supported in balanced way.

Hosted rare disease events in 2011

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 edition⁸² of this initiative was held and co-organised in Istanbul, Turkey.

This excellent collaboration has been also the driving force behind the first ever in Eastern Europe Rare Diseases Summer School for health authorities and legislative bodies, held in Bulgaria on 11-18 September 2011.

The 4th European Symposium on Rare Anaemias⁸³, an ENERCA project activity, was hosted in Sofia on 19-20 November 2011. It was jointly organised by the European Network for Rare and Congenital Anaemias (ENERCA), the Thalassaemics' Organisation in Bulgaria, the Thalassaemia International Federation and supported by the Bulgarian Scientific Society of Clinical and Transfusion Haematology. The event aimed to disseminate up-to-date knowledge and increase the public awareness about congenital and rare anaemias. The 3rd Bulgarian Symposium of thalassaemia patients and professionals was integrated in the framework of the 4th European Symposium on Rare Anaemias. The program included an interactive session with patient panellists and doctors, focusing not only on clinical management but also on prevention and social action for thalassaemia and haemoglobinopathies.

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: EUROGLYCANET and TREAT-NMD.

⁸⁰ www.conf2011.raredis.org

⁸¹ http://raredis.org/pub/Newsletter/Conference_Book_2011.pdf

⁸² <http://www.raredisease2011.org/index.php>

⁸³ <http://www.enerca2011.otbulgaria.com/regform/brochure.pdf>

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 March 2011 reviewing access to medicines for rare diseases in Bulgaria⁸⁴. 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. From 2011, orphan medicinal products reimbursed by the Ministry of Health, the second one by the National Health Insurance Fund (NHIF).

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

All orphan medicinal products, authorised under centralised procedure in EU could be available in Bulgaria, after adoption of the new Regulation N° 10/17 November 2011 for the conditions and the order of treatment with medicinal products without marketing authorisation in Bulgaria, as well for the conditions and the order for including, changes, excluding and distribution of medicinal products from the list in article 266A, paragraph 2 from the Law of medicinal products for human medicine, which replaced Regulation N° 2/10 January 2001. The important change, regarding availability of orphan medicinal products in the Regulation N° 10/17 November 2011 is that it arranged the distribution of the drugs, including orphan medicinal products, that have been priced but are not available on the Bulgarian market or such that have not been priced and included in reimbursement list. Article 266A is new and was enforced from 5 August 2011, arranging the use of the medicinal products authorised in the EU countries that are not distributed on the Bulgarian market.

Currently in Bulgaria, 28 orphan medicinal products with EMA market authorisation are priced and included in the Positive Drug List (PDL) and 22 orphan medicinal products (from the 28 in PDL) are reimbursed at 100% (10 under Ordinance 34 and 6 under Ordinance 38) and should be available for the patients with rare diseases.

The drugs available on the market in 2011 on the PDL and included in Ordinance 34⁸⁵ are: Afinitor, Atriance, Evoltra, Glivec, Litak, Nexavar, Nplate, Sprycel, Tasigna and Torisel. The drugs available on the market on the PDL and included in Ordinance 38 are: Exjade, Fabrazyme, Revatio, Revolade, Somavert, TOBI, Tracleer, Ventavis, Zavesca and Cerezyme.

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.

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 conditions, rules and procedures for regulating and registering the prices of medicines, and it is based on reference pricing, using data from

⁸⁴ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:

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

⁸⁵ Information taken from the report Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria (March 2011):

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

Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal, 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.

Having been priced, orphan medicinal products can be included in the PDL. The Commission on the PDL examines and decides on applications for inclusion, amendments and/or exclusion of drugs from PDL. PDL groups the drugs into 4 annexes: Annex 1 – drugs for treatment, paid under the Health Insurance Act (HIA); Annex 2 – drugs paid by the budget of the medical-treatment facilities under Art. 5 of the Medical Treatment Facilities Act (MTFA) and by the budget of the hospitals with state and/or municipal stake upon Art. 9 and 10 of MTFA; Annex 3 – drugs for treatment outside the scope of HIA, paid in accordance with Art. 82, par. 1, item 8 of the Law on Health; Annex 4 – drugs for treatment of rare diseases, AIDS and infectious diseases. Until the end of 2010 orphan medicinal products in Bulgaria were included in Annexes 3 and 4. From 2011, in conjunction with the new reimbursement schemes, some of them (for rare non-oncological diseases) were transferred to Annex 1 (of medicinal products for treatment, paid under HIA).

Other initiatives to improve access to orphan medicinal products

Changes to Ordinances 34/ 25 Nov 2005 and 38/ 16 Nov 2004 of the Ministry of Health were enforced at the beginning of 2011. The main aim of those changes is to shorten patients' wait for orphan medicinal products. Most of the procedures will be performed by National Health Insurance Fund, instead of Ministry of Health, and the orphan medicinal products will be bought directly, according to price (the orphan medicinal products with respective lowest price will be reimbursed).

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 Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10000 individuals.

National plan/strategy for rare diseases and related actions

The first draft of the National Strategic plan for rare diseases was prepared by the National Steering Committee for rare diseases following numerous meetings and hard work by all involved parties. The National Steering Committee for rare diseases consists of Ministry of Health officials, experts in different fields related to rare diseases and patient representatives.

Initially, in early 2011 a document was prepared by the National Steering committee which consisted of the following three parts: a) a detailed description of the current situation and practices in the field of rare

diseases in Cyprus, b) an extensive analysis of the five chapters to be addressed in the strategic plan, namely prevention, diagnosis, treatment and management, palliative care - social inclusion – supportive measures, registries and research and c) a proposed action plan.

In June 2011 a two-day workshop was organised by this committee with the support and under the auspices of the Ministry of Health. During this workshop, local stakeholders from all areas and fields relevant to rare diseases participated in brainstorming sessions, commented and shared their experiences on the current situation in Cyprus and forwarded their suggestions regarding the development of a National Strategic plan to the members of the National Steering committee. The leader of the Europlan project was invited to address this meeting with a lecture and to share experiences: different working groups reviewed the current situation and the proposed actions for designing a national plan of action for rare diseases. The workshop was a success in the sense that it achieved extensive discussions and active involvement of all participants and ended with a strong conclusive report of strong interest and commitment for active involvement of many, in the future steps for achieving progress and agreement on a National plan of action for rare diseases in Cyprus. The National Steering Committee undertook the responsibility of reviewing the conclusions, comments and suggestions of the workshop in order to enable those that hold the general consensus in the strategic plan. The final draft of the strategic plan will be reviewed once again by the local stakeholders in a second workshop which will take place on the 28 of February 2012 before being finalised and submitted to the Ministerial Council for its final approval. The overall goal is to proceed to the finalising of the proposed strategic plan and its approval by the Council of Ministers within 2012.

Centres of expertise

There are currently no officially designated centres of expertise for rare diseases in Cyprus as there are no criteria or procedures determined yet at the administrative level. Nevertheless there are several institutions which are already functioning at the level of centres of expertise.

The Cyprus Institute of Neurology and Genetics offers diagnosis, treatment and management for various rare neurological and other genetic disorders and has a strong research output. Many research projects on rare disorders have been completed and others are in progress. These include studies on epidemiology, biochemical and molecular characterisation, pathogenetic mechanisms and novel therapies. The Institute is considered a centre of excellence in the fields of neurology and genetics and acts as a referral and training centre for neighbouring countries.

The Archbishop Makarios III Hospital for Mother and Child 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, immunodeficiencies etc. The Clinical Genetics Clinic operating both at Makarios Hospital and the Cyprus Institute of Neurology and Genetics is involved in the management of a large number of patients and their families living with or at risk of a genetic condition.

The Cyprus Thalassaemia Centre is the main centre for screening (premarital), counselling and management of thalassaemia, sickle cell disease and other rare anaemias on the island. The Centre was designated as a WHO collaborating centre in 1985 because of its expertise in community awareness, prevention strategies and educational activities for both patients and medical specialists. 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.

Several specialised clinics and departments in Nicosia General Hospital and other hospitals serve as referral centres for disorders such as rare haematological diseases, rare heart, rheumatologic and immunological disorders etc.

The Center for the Study of Haematological Malignancies was established recently with the aim of offering lifesaving diagnostic and prognostic information which help guide therapeutic decisions and monitoring treatment of rare haematological disorders. The creation of this newly established Center will provide the opportunity for the enhancement of hemato-oncology services in Cyprus and will facilitate the execution of high-impact research in the field of rare hematological malignancies. This centre is housed together with the Karaiskakio Foundation which has the highest per capita ratio of bone marrow donors in the world.

The procedure for officially designating centres of expertise for rare diseases in Cyprus is included as part of the National Strategic plan for Rare Diseases. Hence it is expected that once the strategic plan is approved centres of expertise for rare diseases in Cyprus will be officially designated.

Pilot European Reference Networks

Cyprus participates, or has participated, in the following European Reference Networks for rare diseases: Network of centres of expertise for dysmorphology (Dyscerne), European Network for rare and congenital anaemias (ENERCA) and Together Against Genodermatoses (TAG).

Registries

Several registries have been formed by physicians and 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. Recently, in 2011, 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.

Genetic testing

Genetic testing is available for many rare genetic disorders. This includes chromosomal abnormalities, metabolic disorders, neurogenetic disorders, thalassaemia and other rare hemoglobinopathies, heritable cancers and many others. Genetic testing is available in Cyprus for around 200 genes and an estimated of 100 rare diseases.

National alliances of patient organisations and patient representation

In June 2010, the Cyprus Alliance for Rare Disorders (CARD⁸⁶) 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 announced recently by the Ministry of Health; 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 of 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. In 2011, CARD expanded their awareness programme through the organisation of several educational and informative events. These events had as a focus increasing knowledge about the challenges that rare disease patients face and stress the need for a national plan for rare disorders.

In addition to CARD, numerous patient organisations are active and support and represent patients with rare diseases as well as aim to raise public awareness and improve quality of life of their members.

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 Genetic Department. This team was designated in 2010 as the Orphanet national team for Cyprus by the Medical and Public Health Services of Cyprus. 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. Since December 2011, the national website of Orphanet Cyprus⁸⁷ is operational aiming to provide information on local activities in the field of rare diseases.

Official information centre for rare diseases

Officially there is no information centre for rare diseases apart from Orphanet in Cyprus.

Help line

Currently, there is no dedicated rare disease help line in Cyprus.

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

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

Other sources of information

The Cyprus Institute of Neurology and Genetics is a source of information for several neurological and genetic disorders. Information on rare diseases is also published by Gene Net Cyprus, a project that aims 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 website⁸⁸ () which provides links to Orphanet. Furthermore, the Thalassemia National Centre is the source of information for haemoglobinopathies. Several specialised clinics and organisations are functioning as sources of information for specific disorders.

Good practice 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, such as 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. Furthermore, training and education sessions were organised within meetings of local scientific societies. These included teaching lectures and presentations on rare genetic syndromes, metabolic disorders and rare liver diseases in childhood. In addition, the Cyprus Institute of Neurology and Genetics serves also as a satellite centre to the European Genetics Foundation⁸⁹ courses which include several activities on rare genetic disorders. The Cyprus Thalassemia Centre serves as a satellite centre to ESH courses through ENERCA project.

National rare disease events in 2011

The Cyprus Society of Human Genetics organised a seminar on 24 February 2011 to honour Rare Disease Day. The seminar was addressed by representatives of the Ministry of Health and CARD and was attended by many health professionals, scientists and stakeholders in the field of rare diseases as well as patients and their representatives. In addition, CARD organised a Press Conference on 28 February 2011, in honour of Rare Disease Day, to highlight issues concerning rare diseases in Cyprus.

Hosted rare disease events in 2011

Cyprus hosted a number of rare disease-related events in 2011. These include the Pancyprian Scientific Conference on Rare Diseases organised by CARD in March 2011, the “Together Against Genodermatoses, TAG” International Seminar organized by the Clinical Genetics Department of the Cyprus Institute of Neurology and Genetics and the Makarios III Hospital in November 2011 and the 2nd Thalassemia Conference organized by the Cyprus Institute of Neurology and Genetics and the Pancyprian Antianemic Association in December 2011. Furthermore, as part of specialized medical conferences experts in the management and treatment of GIST, myelodysplastic syndromes and other rare diseases presented the latest advancements in their fields of expertise.

Research activities and E-Rare partnership

National research activities

Funding opportunities for rare disease research (without being specifically ear-marked for this purpose) are offered by the Cyprus Research Promotion Foundation as well as European and International organizations (FP7, Muscular Dystrophy Association, USA and other patient organizations). Telethon is an international charitable institution which is organised by the Cyprus Institute of Neurology and Genetics (CING) to support scientific research on neuromuscular diseases. A large proportion of net revenue (approximately 30%) from the Telethon is allocated to the Association for Patients with Muscular Dystrophy and the rest supports specific research projects conducted at the Institute. The selection of these investigations is made with the help of an independent international scientific committee.

Scientific community in Cyprus is engaged into research activities aiming towards establishing new therapies for a number of rare disorders, in particular gene therapy for rare hemoglobinopathies and neurological disorders. Furthermore, a novel test for non-invasive prenatal diagnosis for Down syndrome which only uses a small amount of blood from the pregnant women was developed and is currently being validated.

⁸⁸ <http://www.genenet.org.cy>

⁸⁹ www.eurogene.org

Participation in European research projects

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

E-Rare

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

IRDIRC

Funding agencies in Cyprus are not yet committed members of the IRDiRC.

Orphan medicinal products

Orphan medicinal product committee

At present there is no orphan medicinal product committee in Cyprus but a dedicated pharmaceutical officer deals with all matters relating to orphan medicinal products in collaboration with treating physicians and Ministry of Health officials.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

No specific information was reported on the orphan medicinal products marketed in Cyprus. Several orphan medicinal products 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 and Pompe disease patients. Other orphan medicinal products were also requested.

Orphan medicinal product pricing policy

No specific activity reported.

Orphan medicinal product reimbursement policy

The Medical Health Services of the Republic of Cyprus cover the cost of orphan medicinal products administered to patients provided that their use is approved by the Pharmaceutical Committee.

Other initiatives to improve access to orphan medicinal products

Reimbursement is available for the compassionate use of orphan medicinal products.

Orphan devices

The Medical Health Services of the Republic of Cyprus cover the cost of orphan devices provided to patients in cases where their use is approved by the relevant Medical Committee.

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) 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 has created dedicated working parties with the aim to establish the basis for the National Action Plan by 2013. A group of stakeholders was gathered in 2011 (including the Ministry of Labour and Social Affairs, experts and payers) and a deadline for elaborating the plan has been established for June 2012.

The Czech ten-year strategy⁹⁰ reveals the budgetary sources for the plan, which will include “existing budgetary chapters and domestic and foreign subsidies” such as the Ministry of Health and the country’s public health insurance. 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 frame of the EEA Norway Grants scheme (2008-2014) for the National Coordination Centre at University Hospital Motol⁹¹ and via annual Ministry of Health targeted appropriation schemes, both which have deadlines in June 2012.

Care for rare diseases is to be concentrated in 10 to 20 centres. The establishment of a National Coordination Centre for rare diseases in the Prague-Motol Teaching Hospital of Charles University Prague⁹² in collaboration with the University Hospital of Masaryk University Brno⁹³ for the sake of regional representation) coincides with the approval of the strategy and creation of the Taskforce. Besides diagnostics and treatment, the strategy will encompass 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. In terms of the establishment of centres for rare diseases, there is an agreement to have one coordinating centre for rare diseases and one in the Moravia region, each accounting approximately for half of the entire Czech population of 10 million inhabitants.

Centres of expertise

There are specialised centres for rare diseases, two of which are the national centre for the diagnosis and treatment of Gaucher disease, and for cystic fibrosis. The value of these hubs 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 reimbursed in these centres and these centres manage the provision of very expensive orphan medicinal products. The organisation of additional specialised centres will be a part of the Czech strategy. Another important and internationally recognised institution is the Institute for Inherited Metabolic Disorders which deals centrally with these diseases at national level. Another important centre for epidermolysis bullosa has been formed as a Czech branch of Debra International at the University Hospital Brno. However, all these centres mentioned above operate based on their professional reputation and could be thus considered as *de facto* centres.

The Czech National Strategy for Rare Diseases foresees the concentration of care for rare diseases in 10 to 20 different centres, with a National Coordination Centre at the Motol Teaching Hospital in Prague, which will coordinate at the regional level with University Hospital Brno. This centre will assure its funding through the Norway Grants scheme by June 2012. Its major aim, beyond structuring the rare diseases field in the country, would be to identify additional *de facto* centres of expertise and propose their transformation into *de iure* centres by the Taskforce. First steps were taken and at their last meeting (November 2011) the Taskforce

⁹⁰ http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf

⁹¹ http://www.mfcr.cz/cps/rde/xchg/mfcr/xsl/Financial_Mechanism_EEA.html

⁹² www.ublg.lf2.cuni.cz

⁹³ www.fnbrno.cz

decided to officially establish three pilot *de iure* rare diseases centres for a) cystic fibrosis⁹⁴, b) metabolic diseases⁹⁵ and c) epidermolysis bullosa⁹⁶, based on a compiled criteria drawn from the published EUCERD and EURORDIS centres of expertise recommendations.

Establishment of centres gives them government recognition, but still does not imply a dedicated budget line. Treatment and diagnostics will thus continue to be provided within standard health insurance procedures administered by a group of health insurance companies. However, in the future and following gradual reform of health care funding (after 2012) it is planned that respective rare diseases or related rare disease diagnostic groups will be concentrated into dedicated centres. In this regard it is expected that the major condition for health care reimbursement would be 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 Reimbursements⁹⁷.

Pilot European Reference Networks

Teams in the Czech Republic participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, EPNET/EPI, ENERCA Paediatric Hodgkin Lymphoma Network, NEUROPED, PAAIR and Care-NMD.

Registries

The Czech Republic contributes to some European registries such as ECFS.eu for cystic fibrosis⁹⁸ and TREAT-NMD for muscular dystrophies, European Porphyria Network (EPNET), EUROCAT for rare birth defects⁹⁹, as well as the SCNIR international registry. The National Registry for Cancer¹⁰⁰ also contains information on the distribution of rare cancers in the Czech Republic. The National Action Plan Taskforce is now 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.

Neonatal screening policy

Neonatal screening is now available for 13 disorders¹⁰¹. 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 Company¹⁰² from 2010. In early 2011 the National coordination centre for neonatal screening was officially established by the Czech Ministry of Health¹⁰³ and its operation is funded by targeted annual appropriation schemes.

Genetic testing

In terms of diagnostic services, there are over 62 molecular genetic laboratories¹⁰⁴ in the country offering DNA testing and 30 cytogenetic laboratories¹⁰⁵. Together, they offer diagnostic tests for more than 518 different rare diseases¹⁰⁶. Genetic counselling exists for all families at risk and 45 such facilities are currently registered¹⁰⁷, 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

⁹⁴ www.cfklub.cz, www.cfrejistr.cz, ublg.lf2.cuni.cz

⁹⁵ www.udmp.cz

⁹⁶ www.debra.cz

⁹⁷ <http://www.cmu.cz/en?Itemid=224>

⁹⁸ www.cfrejistr.cz

⁹⁹ www.vrozene-vady.cz

¹⁰⁰ <http://www.linkos.cz/odbornici/onkologie/nor.php>

¹⁰¹ <http://www.novorozenecky-screening.cz/>

¹⁰² www.vzp.cz

¹⁰³ www.novorozenecky-screening.cz

¹⁰⁴ <http://www.slg.cz/pracoviste/molekularni-genetika/>

¹⁰⁵ <http://www.slg.cz/pracoviste/cytogenetika/>

¹⁰⁶ This information is provided by <http://www.slg.cz/pracoviste/vysetreni/>

¹⁰⁷ <http://www.slg.cz/pracoviste/klinicka-genetika/>

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. 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”¹⁰⁸. Moreover, new law 372/2011 Sb stipulates provisions regarding informed consent procedures in the domain of health care services.

National alliances of patient organisations and patient representation

In December 2011 foundations were established for the creation of an overarching Czech National Alliance for Rare Diseases¹⁰⁹. This alliance will link together other patient support groups via a democratic, bottom-up, activity spearheaded by several larger patient support groups. Its registration with the Ministry of Interior is expected to be completed by May 2012, including establishment of its bylaws and governance structure. This association plans to join EURORDIS and participate in its activities. Creating an alliance for rare disease patient groups is a provision of the national strategy being developed, together with the Coalition for Health Association¹¹⁰. The Coalition for Health Association includes all diseases, while the Czech National Alliance for rare diseases will collaborate on topics of common interest. However, there are 43 patient organisations in the Czech Republic. Some groups benefit from aid from the Ministries of Health and of Labour and Social Affairs; the system will be streamlined under the National Action Plan, since representatives of the Coalition for Health are members of its Taskforce. Following official registration of the Czech National Alliance for Rare Diseases its representatives will be included in the Taskforce.

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. 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 website¹¹¹ in the Czech language providing an entry point to the database.

Official information centre for rare diseases

There is no official information centre for rare diseases in the Czech Republic other than Orphanet: however its creation is envisaged by the National Action Plan Taskforce, together with a dedicated website¹¹².

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.

Other sources of information

Patient organisation web sites are one of the few national sources of information for rare diseases in the Czech language. It is expected that the National Alliance for Rare Diseases will foster their links and best practice. A web based information service on neonatal screening is available¹¹³.

Good practice guidelines

Best practice guidelines for genetic diagnosis are listed at the National Reference Laboratory for DNA diagnostics at the Institute of Haematology and Blood transfusion for the more common rare diseases¹¹⁴ and reflect EMQN, CMGS and Eurogentest.org guidelines.

Training and education initiatives

No specific activity reported.

¹⁰⁸ <http://www.oecd.org/dataoecd/43/6/38839788.pdf>

¹⁰⁹ www.vzacna-onemocneni.cz/

¹¹⁰ www.koaliceprozdravi.cz

¹¹¹ <http://www.orphanet.cz/national/CZ-CS/index/%C3%BAvod/>

¹¹² The site www.vzacnenemoci.cz is under construction.

¹¹³ <http://novorozenecky-screening.cz>

¹¹⁴ <http://www.uhkt.cz/nrl/nrl-dna/blp>

National rare disease events in 2011

Amongst the rare disease events hosted by the Czech Republic in 2011 were the Metabolic Days¹¹⁵ (Mikulov, 11-13 May 2011), Czech National Genetics Meeting¹¹⁶ (Třeboň, 7-9 September 2011) and the Czech National DNA diagnostics conference¹¹⁷ (Prague, 24-25 December 2011).

Hosted rare disease events in 2011

No rare disease events hosted by the Czech Republic in 2011 were reported.

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, NEUROSIS, PNSEURONET, RD PLATFORM, SARS/FLU VACCINE, SCRIN-SILICO and SIOPEN-R-NET. Teams in the Czech Republic contribute to the following European registries: EURO CARE CF, EURO CAT and TREAT-NMD.

E-Rare

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

IRDiRC

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

Orphan medicinal products

SUKL¹¹⁸, 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 incentives¹¹⁹

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*”

¹¹⁵ www.dedicnemetabolickeporuchy.cz/

¹¹⁶ www.trebon2011.slg.cz/

¹¹⁷ www.dnakonference.cz

¹¹⁸ www.sukl.cz

¹¹⁹ 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)

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.¹²⁰”

Orphan medicinal product pricing policy

No specific information reported.

Orphan medicinal product market availability situation

In January 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, Firazyf, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedea, Peyona, Prialt, Replagal, Revlimid, Revolade, Somavert, Tasigna, 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, Firazyf, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedea, Peyona, Prialt, Replagal, Revlimid, Revolade, Somavert, Tasigna, Tepadina, Torisel, Tracler, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Yondelis, Zavesca). In some cases the level of reimbursement is according to individual negotiation between centres and marketing holders.

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.

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.

¹²⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (pp9-10)*

1.6. DENMARK

Definition of a rare disease

There is no official absolute definition for rare diseases at the moment in Denmark. The National Board of Health tends to define rare diseases as affecting no more than 500 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.

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 national/strategy plan for rare diseases in Denmark involving all sectors, but regarding the hospital sector the Danish National Board of Health 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 catalogue of centres of expertise designated by the National Board of Health. This catalogue 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 describes 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 Diseases¹²¹ in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark. During 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 has a broad representation of stakeholders, to elaborate a national plan for RD, was founded at the end of 2011 and met at the start of February 2012 for the first time. The recommendations in previous report on rare diseases from 2001 will be 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.

Centres of expertise

The National Board of Health 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 is also a number of other

¹²¹http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_denmark_europlan.pdf

established referral centres/centres of expertise approved by the National Board of Health to maintain a specific or several specific rare diseases¹²².

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.

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 specialized treatments. In 2010 the National Board of Health announced the approved hospital departments.

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 this new National Plan for highly specialized hospital services issued about 1100 approvals of medical highly specialized 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.

Pilot European Reference Networks

Danish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPI, NEUROPED, Paediatric Hodgkin Lymphoma Network, PAAIR, EN-RBD and Care-NMD

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. Up to 2010 there is collected data on 1800 patients with 561 different diagnoses seen at 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 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.

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

¹²² For more information: *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/RDTFCR2006.pdf>

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 National Board of Health.

Diagnostic tests are registered as available in Denmark for 139 genes and an estimated 205 diseases in the Orphanet database¹²³.

National alliances of patient organisations and patient representation

Rare Disorders Denmark (RDD), founded in 1985, is the national alliance of 43 rare disease patient organisations/societies. In addition there are further 20 other patient organisations for rare disorders. Patient organisations are eligible to receive limited funding from the Ministries of Health and Social Affairs and have an obligation to capacity build in order improve integration of patients in schools and at the work place. RDD has a small professional body of staff, in cooperation with the Danish Haemophilia Society. RDD facilitates exchange of experience between the member societies and advocate the rights of all rare disease patients.

Rare Disorders Denmark has developed a tool, Social Profiles, to promote dialogue between rare disease patients and professionals. The profiles are currently available for 23 rare diagnoses, with more to come. The profiles are published on the “Rare Citizen” website¹²⁴.

Rare Disorders Denmark RDD holds a mini-roundtable with relevant pharmaceutical companies. The mini-roundtable has 8-10 members.

In 2011, RDD had the following main activities:

1. Lobbying for a national plan for rare diseases and handicaps. In May 2011, RDD published and disseminated a booklet about the importance of a national plan and throughout the year met with politicians and civil servants to promote the forming of a working group.
2. Developing a special training programme for rare disease families with children under the age of 18 – “Rare Family Days”. In the framework of a randomised study, two family courses were conducted for 16 families. The results will be published in 2012, along with a new concept for “Rare Family Days”.
3. Cooperating with the Centre of Disability and Social Psychiatry (ViHS) to transfer a Focus Point of Contact for very rare disease patients and relatives with no possibility to join or form a patient organisation/society. RDD built and ran a temporary website for dialogue between the members of the Focus Point and prepared to fully take over the Focus Point in 2012.
4. In June 2011, RDD participated in the EURORDIS POLKA project as a work package leader: among other activities, RDD performed a survey in cooperation with the Centre of Expertise in Aarhus, University Hospital of Skejby. The aim of the survey was to discover the perception of the quality and more of the Centre from health care professionals and rare disease patients.

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

¹²³ Information extracted from the Orphanet database (September 2011).

¹²⁴ www.sjaeldenborger.dk

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*¹²⁵) 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 Rarelinc.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*¹²⁶) as of 1 January 2011. In October 2010, the Minister for Social Affairs met with the Centre for Rare Diseases and Disabilities (*Center for Små Handicapgrupper – CSH*) and Rare Disorders Denmark concerning this merger. The plans have been met with concern regarding the continuation of the services provided by CSH. The experience of the first year of the new structure is that the help line is functioning well, but 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

Up until 2010 CSH ran a rare disease help line which provided information and support. As a result of the reorganisation of the CSH, there is established a dedicated “Rare Disability Team” within the ViHS’s counselling service which mans the help line from January 2011 onwards.

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 of other health care professionals, families, teachers and caretakers.

National rare disease events in 2011

To mark Rare Disease Day 2011, Rare Disorders Denmark encouraged policy makers and others stakeholders to become friends of the Day. In addition, the alliance launched a new feature on its website, “Rare stories”. This section gives patients, caregivers and others interested in rare diseases the opportunity to tell their own story and share it with others¹²⁷. In addition, in November 2011, a nordic conference about Huntingtons Disease was held in Copenhagen.

¹²⁵ www.csh.dk

¹²⁶ 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)

¹²⁷ www.sjaeldnediagnoser.dk/historier

Hosted rare disease events in 2011

In 2010 the following rare disease events were announced in *OrphaNews Europe*: VI Cornelia de Lange Syndrome World Conference (27-31 July 2011, Copenhagen), European Conference on Post Polio Syndrome (31 August – 02 September 2011, Copenhagen).

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, EMVDA, EUNEFRON, HDLOMICS, HUE-MAN, HUMALMAB, 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 currently an E-Rare partner.

IRDiRC

Danish funding agencies are not currently committed members of 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 products¹²⁸.

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 medicines¹²⁹. 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, Elapraxe, 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.

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-payment¹³⁰.

¹²⁸ 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)

¹²⁹ www.medicinpriser.dk

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)¹³¹.

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

There is currently no plan for rare diseases in Estonia. 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 2012 a working group will be set up to discuss the activities on the field of rare diseases which will be added to the implementation plan of ERTA.

Centres of expertise

Up to Summer 2011 there were two clinical genetics centres specialising in the diagnosis and treatment of rare diseases in Estonia, Tartu University Hospital and Tallinn Children's Hospital. 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. 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 all over Estonia.

Pilot European Reference Networks

Estonian teams participated, in the following European Reference Network for rare diseases: PAAIR.

¹³⁰ *EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, C. Habl & Florian Bachner, p.47.

¹³¹ 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)

Registries

Estonia does not have national registers for groups of diagnoses separately. In Estonia all health-related information is collected to the Tervise Infosüsteem (Health Information System). In case of need there is possibility to extract the necessary information. Estonia participates in the EURO CARE 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 prevention¹³². 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 and congenital hypothyroidism since 1993.

Genetic testing

Genetic testing for 46 different diseases is currently available at the Department of Genetics at Tartu University Hospital¹³³. Diagnostic tests are registered as available in Estonia for 160 genes and an estimated 78 diseases in the Orphanet database¹³⁴.

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 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, here is a dedicated Orphanet team in Estonia, currently hosted by the Estonian Biocentre. The team was designated at the Orphanet team for Estonia by the Ministry of Social Affairs 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. In 2011 the Orphanet Estonia national website¹³⁵, 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

No specific information reported.

Good practice guidelines

No specific information reported.

¹³² <http://www.kliinikum.ee/geneetikakeskus/>

¹³³ See the regularly updated list in Estonian for further information: <http://www.kliinikum.ee/geneetikakeskus/>

¹³⁴ Information extracted from the Orphanet database (September 2011).

¹³⁵ <http://www.orpha.net/national/EE-ET/index/avaleht/>

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). In 2009 -2011 the number of 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 (i.e. a new course is planned for 2012).

National rare disease events in 2011

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.

Hosted rare disease events in 2011

The 11th annual International GeneForum¹³⁶ was held on 10-11 June 2011, in Tartu, Estonia. This conference on genetics and genomics brought together experts from Europe and the United States of America for discussion on the progress in the field of genetics and in particular, on interdisciplinary areas within human genetics, epigenetics, modern population genetics, biomedical informatics and personal medicine. The conference also incorporates an exhibition aimed at biotechnology-related companies.

The second OpenGENE Young Investigator Workshop in the Baltic Region was held in Tartu, Estonia, on 23-26 August 2011 and focused on re-sequencing, genotyping and statistical analysis of common complex diseases.

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 available over four years)¹³⁷. 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.

¹³⁶ <http://www.geneforum.ee/GF2011/index.php>

¹³⁷ 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)

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 Ravimiamet¹³⁸ (*State 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. Currently¹³⁹ *Haigekassa* reimburses patients 100% of the costs of 21 orphan medicinal products.

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.

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 Foundation¹⁴⁰ 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 2011, 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.

¹³⁸ <http://www.sam.ee/>

¹³⁹ Information accurate in December 2011.

¹⁴⁰ <http://www.agrenska.ee/>

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.

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). 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, including hospital districts, governmental institutes like the National Institute for Health and Welfare, the Orphanet National Advisory Board, the umbrella organisation for rare diseases HARSO 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).

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 conclusion¹⁴¹ 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.

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.

Pilot European Reference Networks

Finnish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET and EPI.

Registries

In general, all the main health care registries are under the National Institute for Health and Welfare.

There are two legally specified registries concerning rare diseases: the Finnish register of congenital anomalies and the Finnish register of visual impairment.

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

¹⁴¹ <http://www.nordicwelfare.org/filearchive/1/119089/Rapport%20med%20bilagor%20final.pdf>

primary and specialised health care¹⁴²) 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. 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 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. 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, a private laboratory Medix Laboratories Ltd offers a selection of genetic tests.

There are no national guidelines for performing genetic testing. 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.

Genetic tests are, as a rule, performed in the framework of public health care. The municipalities then are responsible for paying for the tests. 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 tests are often purchased from abroad. 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 158 genes and an estimated 195 diseases in the Orphanet database¹⁴³. 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 planned for 21 January 2012.

The role of the new alliance is yet to be seen. 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, currently hosted by the Medical Genetics Clinic of Vaestoliitto, the Family Federation of Finland. 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 research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database, as well as maintaining the Orphanet Finland national website¹⁴⁴ in Finnish.

In 2010 Orphanet and Terveystieto¹⁴⁵ established a collaboration. Terveystieto is maintained by Duodecim, the Finnish Medical Society, a scientific society adhered to by almost 90% of Finnish doctors and

¹⁴² www.thl.fi/tietokantaraportit

¹⁴³ Information extracted from the Orphanet database (September 2011).

¹⁴⁴ <http://www.orpha.net/national/FI-FI/index/kotisivu/>

¹⁴⁵ <http://www.terveysportti.fi/>

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. During 2010 links from Terveysportti's Finnish texts to the Orphanet disease 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.

Official information centre for rare diseases

There is no official information centre for rare diseases in Finland other than the services provided by Orphanet.

Help line

There is no official help line for rare diseases. The Medical Genetics Clinic of Vaestoliitto, the Family Federation of Finland has a nationwide phone and e-mail service for matters concerning rare diseases, which operates on work-days.

Other sources of information

Established in 1993, the Harvinaiset Network is a network of 17 non-governmental, non-profit organisations funded by RAY, Finland's Slot Machine Association. 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

Information on 35 monogenic diseases belonging to the Finnish Disease Heritage¹⁴⁶ 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.

Training and education initiatives

No specific information reported.

National rare disease events in 2011

Rare Disease Day 2011 was coordinated by the Finnish Network for Rare Diseases, Harvinaiset. Awareness raising campaigns were launched on the website harvinaiset.fi and in social media between 25 and 28 February 2011 in cooperation with local associations and groups. Stories, photos, videos and messages around the theme "rare but equal" were shared. The members of the Finnish Network for Rare Diseases visited schools, institutions and other focus groups to inform about the RDD and issues concerning rare diseases. Members of the Network also launched their own press releases concerning the day.

On 21 October 2011, a rare disease event was organised in Helsinki by medical specialist societies and Swedish Orphan Biovitrum. 150 health professionals, researchers and policy makers attended. The main theme of the meeting was rare disease research and treatment, the current situation and future possibilities. Special national funding into research was requested because funding possibilities have diminished in recent years. Much of the general discussion focused on the assessment of marketed drugs for reimbursement but also on

¹⁴⁶ <http://www.findis.org/main.php?action=disease>

the need for centres of expertise, and involvement and empowerment of patients and their families to the RD field. A 700 name petition was handed over to the minister of Social Affairs and Health. The petition drew attention to the unequal situation of rare disease patients compared to common disease patients.

On 20 October 2011 the Orphanet Finland team organised a one-day meeting for the Orphanet National Advisory Board members which focused on the national plan for rare diseases and allowed members to express their expectations for the plan. Discussion also focused on how to structure centres of expertise in Finland, including their criteria, funding, role of the university hospitals and importance of the research in the context of centres etc. Importance of networks and cooperation between specialists in various fields were highlighted in many speeches.

Hosted rare disease events in 2011

No specific information reported.

Research activities and E-Rare partnership

National research activities

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, EUGINDAT, EUMITOCOMBAT, EURAPS, EUREGENE, EUROBOBNET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, GEN2PHEN, LYMPHANGIOGENOMICS, NEUROPRION, PEROXISOMES, PROTHETS, 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 incentives¹⁴⁷

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.

¹⁴⁷ 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)

Orphan medicinal product market availability situation

Of the orphan medicinal products with EU market authorisation, 48 are available on the market currently in Finland in at least one form, if not in all forms. The Fimea¹⁴⁸ lists the following orphan medicinal products as available on the market in Finland: Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Increlex, Inovelon, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedea, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, 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*¹⁴⁹ 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

According to the 2005 *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹⁵⁰ in the section concerning Finland, "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 42% of the purchasing price. In certain diseases or conditions, lower (72%) or higher (100%) special reimbursement is available.

In October 2010 Harvinaiset, the Finnish Network for Rare Diseases, sent a letter¹⁵¹ 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 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.

Orphan devices

No specific information reported.

¹⁴⁸ <http://www.fimea.fi/medicines/fimeaweb>

¹⁴⁹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p12)*

¹⁵⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p12)*

¹⁵¹ http://harvinaiset.fi/ajankohtaista/stm-n-vastaus-kannanottoon-laeaekehoidon-korvauksista&rurl=translate.google.fr&twu=1&usg=ALKJrh-90epLiXoahxcmk5V47DHOlr_Av

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 2005-2008, adopted at the end of 2004, with allocated funding. This first plan 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 rare diseases 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 (called "*Centre de compétences maladies rares*" which are the equivalent of regional centres of expertise). 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 helpline for patients (called "*Maladies Rares Info Services*" – MRIS¹⁵², the French rare disease information service helpline) was developed. Several new information products for health professionals were developed such as emergency guidelines and clinical practice guidelines (called "*protocole national de diagnostic et de soins*" – PNDS – "*national diagnosis and treatment protocol for a rare disease*"); all these guidelines are published on the Orphanet website. Emergency cards to be used by the patients in case of need were also produced.

Funding for this 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 five year period).

¹⁵² <http://www.maladiesraresinfo.org>

Evaluation of the First Plan

The first French National Plan for Rare Diseases underwent intense scrutiny when its five-year term ended in 2008. The main goal of the evaluation of the plan was to provide data to serve for the elaboration of a second plan, initially expected in 2010. An Evaluation Committee consisting of health, economic 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 five 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 the 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 MRIS), 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 need to be reformulated taking stock of the difficulties encountered and defining 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 report¹⁵³ was completed by a self-assessment report¹⁵⁴ 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 patient organisation stakeholders who 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 Maladies Rares, in collaboration with EURORDIS, organised a national conference on rare diseases¹⁵⁵ in the context of the Europlan project. The theme of the conference was “The French plan in the European landscape”. This conference 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 Diseases¹⁵⁶ was elaborated by the Ministry of Health during 2009-2010 from the results of the evaluation of the first plan and from the conclusions of seven working groups, which had gathered during 34 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. 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 French Reference Centres;
- Improvement of access to biological and 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 to patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

¹⁵³ http://www.hcsp.fr/docspdf/avisrapports/hcspr20090317_maladiesRares.pdf

¹⁵⁴ http://www.sante.gouv.fr/IMG/pdf/Evaluation_interne_Plan_National_Maladies_Rares_2005-2008.pdf

¹⁵⁵ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_france_europlan.pdf

¹⁵⁶ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

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*”¹⁵⁷);
- Creation of a National Rare Disease Database (called “*Banque Nationale de Données Maladies Rares*” or BNDMR) to allow mapping of patients’ needs and healthcare delivered, and facilitate their recruitment for clinical trials;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature;
- Organisation of 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 molecular diagnosis for a large set of rare diseases. Various levels of NGS will be developed during the plan for maximal diagnosis coverage;
- Restructuring of rare disease Reference and Competence Centres into a limited number (around twenty) of coherent “clinical networks” (called “*filières maladies rares*”), gathering all rare disease relevant stakeholders and centered on a homogeneous group of 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 networks for rare diseases.

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

- Setting up of a permanent working group for the monitoring of rare disease Reference Centres and future reference networks;
- Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed out of their marketing authorisation;
- Enhancement of clinical practice guideline development;
- Training of medical doctors and paramedical professionals;
- Coordination of health care and social care.

The implementation of the second plan is the mission of a dedicated Steering Committee (called the “*Comité de suivi et de prospective*”) which held its first meeting on 19 May 2011. Five thematic working groups reporting to the Steering Committee were established to help implementing the plan. These include a permanent group dedicated to the monitoring of Reference Centres and their future networks. The Steering Committee is in charge of the follow up of the plan and making sure that the implementation of the plan is on schedule, of the effective involvement of relevant bodies and institutes in the implementation, and of surveying new methods of diagnosis, prevention, treatment and care for patients with rare diseases.

In addition to this, the evaluation of this second plan will soon be considered, and before the end of 2013 a third plan will be discussed to extend this work.

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

A second national plan for cancers¹⁵⁸ was announced on 2 November 2009 for the period 2009-2013. This plan follows a first plan¹⁵⁹ covering the period 2003-2007, and includes rare cancers. The six main measures of the plan are: research, observation, prevention, screening, care, and living with and after cancer. The plan specifically aims to develop specialised care for patients with rare cancers, including the labelling of “reference centres for rare cancers”.

The National Cancer Institute (*Institut National du Cancer – INCa*) has 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 situation of patients in France. The report was published at the same time as a new web portal on cancer data on the INCa site¹⁶⁰. The INCa also released at the end of 2011 its first report on the activity of expertise for rare cancers of adult patients, including updates on their organisation, collaborations, translational research and clinical trials, survey of cases in national databases, and elaboration of recommendations for rare cancers amongst other actions¹⁶¹.

¹⁵⁷ The “Fondation Maladies Rares” was created in February 2012: <http://fondation-maladiesrares.org>

¹⁵⁸ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

¹⁵⁹ <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

¹⁶⁰ <http://lesdonnees.e-cancer.fr/>

¹⁶¹ <http://www.e-cancer.fr/toutes-les-actualites/360/6714-synthese-de-lactivite-2010-des-centres-experts-cliniques-pour-cancers-rares-de-ladulte>

French National Plan for Rare Disabilities 2009-2013

A plan aimed at rare disabilities (of which rare diseases can be a cause) was adopted on 27 October 2009 for the period 2009-2013¹⁶². The National Solidarity Fund for Autonomy (*Caisse Nationale de Solidarité pour l'Autonomie* – CNSA) is in charge of implementing this plan. According to this plan (“National Scheme for Rare Disabilities”), the definition of a “rare disability” is the coexistence of prevalence of no more than 1 in 10 000 people, 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 evolution 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 interregional relays;
- The development of the offer of services at home and in establishments for patients with rare disabilities.

Measures of the plan include the creation of 300 additional places in care centres, regional relays, and national “resource centres”. Three national “resource centres” were created for patients with a visual or hearing deficiency associated with other deficiencies or diseases. A national “resource centre” for patients with rare disabilities and severe epilepsy will be created soon in 2012. A national “resource centre” for patients with rare disabilities and behaviour disorders is in project. Cooperation between national “resource centres” for rare disabilities and “reference centres” for rare diseases is 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 about this rare disease. In 2011, the evaluation of this plan began in the perspective of a next third plan.

In June 2008, a national plan concerning visual handicap (of which rare diseases can 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 handicap¹⁶³.

In February 2010, a national plan concerning deafness and hearing-impairment (of which rare diseases can be a cause) for the period 2010-2012 was published¹⁶⁴, 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 to make social life more accessible to them.

A system of digital, personal medical record (called the “Dossier Médical Personnel” – DMP) was relaunched in 2009 in France and began to be operational in 2010¹⁶⁵ with further deployment in 2011. This initiative will hopefully ensure a more efficient medical follow-up for patients, among them rare disease patients. The DMP will facilitate communication of information between the different specialists, GPs and centres of expertise involved in the follow-up of rare disease patients.

The French National Authority for Health (*Haute Autorité de Santé* – HAS) and the French Biomedicine Agency (*Agence de la Biomédecine*) signed a collaboration on 14 December 2010¹⁶⁶ to work together during 3 years on project to improve healthcare in four fields in which the *Agence* is principally involved: organ donation, transplants, medically assisted reproduction and human genetics.

On 25 January 2011 the Minister of 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 for instance of therapeutic research or better understanding of the condition.

In 2011, the web portal “Epidemiology – France”¹⁶⁷ was launched, aiming to provide a directory of databases to advance research and expertise in the field of health in France. The initiative is supported by the INSERM (French National Institute for Healthcare and Medical Research), the National Competitiveness,

¹⁶² http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf; http://www.cnsa.fr/article.php3?id_article=726

¹⁶³ http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUN08.pdf; www.cnsa.fr/IMG/doc/Plan_handicap_visuel_1_-2.doc

¹⁶⁴ http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan_en_faveur_des_personnes_sourdes_ou_malentendantes_-_10_02_2010.pdf

¹⁶⁵ http://esante.gouv.fr/sites/default/files/CP_OuvertureServiceDMP_141210.pdf. In March, 2012, 100 000 DMP were created.

¹⁶⁶ 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

¹⁶⁷ <http://epidemiologie-france.fr/>

Industry and Services Directorate of the French Ministry of the Economy and the LEEM (French Pharmaceutical Companies Union). It brings together information on around 300 databases and includes a search by the theme “Rare Diseases”, which includes mostly nationally designated registries.

Centres of expertise

The first National Plan for Rare Diseases (2004-2008) introduced a structured organisation of healthcare for rare disease patients. A designation process was created to name centres of scientific and clinical excellence in the field of rare diseases. By the end of the plan, 131 “Reference Centres” were named by the French Minister of Health and received a specific financial support for their missions. These centres have 6 main missions:

- To facilitate diagnosis and define the course of treatment;
- To define and publish national clinical practice guidelines for rare diseases (pnDs) in collaboration with the *haute autorité de santé* (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 of prevention and health education (*institut national de prévention et d’éducation pour la santé – inpes*);
- To coordinate networks of health visitors and social workers;
- To be the contact point for patient organisations and social workers. Each centre has a double role: it is an expert centre for 1 or more diseases for which it is labelled, and it is a resource centre for patients referred to it.

The reference centres are evaluated over time, first through self-evaluation after 3 years as a designated centre, then with an external evaluation at 5 years. The external evaluation is organised by the HAS published its 2010 activity report in 2011, with one section dedicated to its activity in the evaluation of reference centres¹⁶⁸. During the first plan, a National Consultative Designation Committee (*Comité National Consultatif de Labellisation*) analysed the results of the external evaluation and gave advice to the Ministry of Health. This Committee has not been continued. The new designation process is still in progress. It will probably be based on the permanent working group set up during the second plan to monitor Reference Centres and their future clinical networks.

A second type of centres was designated in 2008: named “Centres de compétences” (Regional Centres), these qualified centres were identified by each Reference Centre and designated by 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. The regional centres have not received specific financial support for their activities, and they are not included in the evaluation process of the reference centers. These qualified regional centres take in charge patients from their region: 500 of these centres have been named corresponding to 1 centre per region in each of the large categories of reference centres.

Rare cancers had been excluded from the first national plan for rare diseases (2004-2008) as a national plan for cancer including measures for rare cancers was already in place. The National Cancer Institute (*Institut National du Cancer - INCA*¹⁶⁹) published a report¹⁷⁰ on the advances made in the structuring of the health care offer for rare cancers, which was one of the key measures of the Second National Cancer Plan (2009 -2013): this includes the creation of a system of national “reference centres” and regional “competence centres” for rare cancers. As of 2009, 15 “rare cancer centres” have been designated and four reference networks have been set up. These designated centres receive financial support.

Three resource centres for rare disabilities have been designated in 2011.

In 2011 the Hospitals of Angers and Nantes in association with the French Alliance for Rare Diseases created a platform to support patients with rare disease in the Pays de la Loire region. This unique platform composed of a team including neurologists, a dermatologist, a psychologist, an occupational therapist, a social worker and a coordination assistant, will help patients to find their way in the health and social care system.

An experimental programme is underway in Montpellier to provide support to patients with rare disease and training sessions to professionals of health and social sector. This action is set up with the partnership of the French Alliance for Rare Diseases and centres of expertise settled in the area.

¹⁶⁸ http://www.has-sante.fr/portail/jcms/c_1070314/rapport-annuel-d-activite-2010

¹⁶⁹ <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

¹⁷⁰ <http://www.e-cancer.fr/toutes-les-actualites/360/6714-synthese-de-lactivite-2010-des-centres-experts-cliniques-pour-cancers-rares-de-ladulte>

Pilot European Reference Networks

France participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET/EPI (main partner), EUROHISTIONET (main partner), NEUROPED, Paediatric Hodgkin Lymphoma Network, EN-RBD, and TAG (main partner).

Registries

The 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 is aimed 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 suitability of the envisaged means for managing registries;
- helping to diffuse and valorise information produced by qualified registries.

Members of the Committee include official members (French Institute For Public Health Surveillance, French National Institute of Health and Medical Research, Ministry of Health etc.) and professionals with expertise in the field of rare diseases or public health, and representatives of patient organisations. They are nominated for a 3- year term. In December 2008, 6 registries were qualified by the National Rare Disease Registry Committee for the period 2009-2011. Three new national registries were qualified in 2010 for the period 2011-2013 for the following rare diseases: esophageal atresia, arterial pulmonary hypertension and hereditary immune system disorders. In December 2010¹⁷¹ a new representatives of professionals were nominated to the National Rare Disease Registry Committee. A new call for proposals was launched in 2011 as each year. A new set of seven national registries were qualified for the period 2012-2015 for the following rare diseases: thalassemia, Gaucher disease, congenital neutropenia, Pompe disease, cystic fibrosis, histiocytosis, and biliary atresia.

The Second National Plan for Rare Diseases foresees the creation of a National Rare Disease Database (BNDMR) containing a minimal data set to be filled in concerning rare disease patients in order to collect a minimum amount of common information.

The French Institute for Public Health Surveillance (*Institut de Veille Sanitaire*) 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 online¹⁷².

France contributes to European registries including EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, the European central hypoventilation syndrome registry, EIMD, EUROWABB, EUROTRAPS, CHS, EURO CARE CF, ECFS, INFEVERS and TREAT-NMD.

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, and 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 HAS. The HAS recommends the extension of the screening programme to medium chain acyl-CoA dehydrogenase deficiency. The decision to put this recommendation into practice has not yet been taken. That requires reorganising first the whole neonatal screening programme because tandem mass spectrometry cannot replace all the existing screening techniques, and cannot be used in all the laboratories which currently participate 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 for deafness (of which rare diseases can be a cause), on which the HAS had given recommendations in 2007, will be launched in a near future.

¹⁷¹ <http://www.legifrance.gouv.fr/affichTexte.do?dateTexte=&categorieLien=id&cidTexte=JORFTEXT000023386975&fastPos=1&fastReqId=1558215089&oldAction=rechExpMesuresNominatives>

¹⁷² <http://www.invs.sante.fr/surveillance/index.htm> (Section “Maladies Rares”)

Genetic testing

The French Biomedicine Agency (*Agence de la Biomédecine*), a public organisation operating under the supervision of the Minister 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 2010 annual report¹⁷³ in 2011. For the second consecutive year, the Agency includes data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The annual report reveals that 361 169 tests were performed in France in 2010, including 11 564 pharmacogenetic tests (3.2%) – an area of increasing activity. The data come from 236 laboratories, representing 98% of the total laboratories included in the survey. Of these, 75 have at least one cytogenetic activity (including molecular testing) and 188 have at least one molecular genetic activity. In the domain of molecular genetics (including pharmacogenomics), diagnostic tests were undertaken for 950 diseases (of a total offer of 1 084 diseases for which testing is possible in France). Of the 950 diseases tested, 665 tests are available in only one laboratory in the country. The tests involved nearly 1 100 different genes. Two indications (hemochromatosis and non rare thrombophilia) represented over 40% of the total analyses conducted in 2010.

There were also 70 997 karyotype analyses performed in 2010 and 13 928 in situ hybridisation (FISH). The percentage of abnormalities (balanced and unbalanced) diagnosed by postnatal cytogenetic karyotype in 2010 was 8.4% for intellectual deficit and malformation syndromes, 3% for reproductive disorders, 13% for chromosome breakage syndromes, and 13.9% for family studies.

In the arena of prenatal diagnosis (PND), of the 35 783 cases examined in 2009, 6 993 certificates were issued for a medical termination of pregnancy (MTP). Of these, 578 pregnancies were pursued although a MTP had been issued. Among MTP cases, 43.1% were for malformations or malformation syndromes, 39.2% for chromosomal abnormalities, 5.4% for genetic abnormalities, 3.2% for maternal conditions, and 1.4% involved infections.

Ultrasound is the most practiced 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, the number of medically 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 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 2010 report of the Biomedicine Agency demonstrates that France continues to be a model for other countries in terms of the range of its genetic test offered, its healthcare coverage in this area, and its remarkable transparency of data.

Diagnostic tests are registered as available in France for 1 129 genes and an estimated 1 092 diseases in the Orphanet database¹⁷⁴.

The final text of the Bioethics Law¹⁷⁵ 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.

¹⁷³ http://www.agence-biomedecine.fr/uploads/document/RA_BIOMED_2010_Internet.pdf

¹⁷⁴ Information extracted from the Orphanet database (September 2011).

¹⁷⁵ <http://www.service-public.fr/actualites/001820.html>;

<http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024323102&dateTexte=&oldAction=rechJO&categorieLien=id>

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. This alliance played a major role in the elaboration of the first and second National Plan and in the evaluation of the reference centres. The French Rare Disease Alliance celebrated its 10 anniversary in 2010 and marked the occasion with a reunion 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 to rare diseases to make it available in centres of expertise for rare diseases and for members of the Alliance. The guide is destined to patients and their families, and provides information on the organisation of expert care and the services in place for patients and their families. The guide also gives information on the organisations of patients with rare diseases 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 patient organisations have received some public funding during the first and second plans for various support activities and awareness campaigns.

Sources of information on rare diseases and national help lines

Orphanet activities in France

In terms of public information measures, support for the French Rare Disease Platform (*Plateforme Maladies Rares*, established in 2001 in Paris), and more particularly for the Orphanet web portal on rare diseases, has been reinforced under the two National Plans, and has been designated by the Ministry of Health in the upcoming Orphanet Joint Action financed by the European Commission.

Orphanet was established in 1997 and is the reference for all rare disease information in France. The team, hosted by the INSERM in Paris, is in charge of collecting data on services for rare diseases (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) for 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 France¹⁷⁶ national website. A new more user-friendly version of Orphanet portal was launched in 2008 with additional features. 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 CNSA (French Agency in charge of the autonomy of the elderly and disabled people '*Caisse Nationale de Solidarité pour l'Autonomie*') and is in charge of leading a project in the framework of the National Scheme for Rare Disabilities to develop the information available concerning such situations, and to make rare diseases and rare disabilities visible in the disability coding systems. Orphanet will introduce specific chapters on disability in the General Public encyclopedia concerning rare diseases leading to disability, whether this disability is 'rare' or not. Orphanet will also provide methodological support to resource centres for rare disabilities (three such centres exist today in France) in order to help them produce good practice guidelines for paramedical and social care of patients with rare disabilities. 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. This 3-year cooperation is an opportunity to develop information on some crucial aspects of rare diseases that have not been addressed specifically before in Orphanet. This information will be useful to patients, families and professionals dealing with disabilities.

Official information centre for rare diseases

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

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 a series of internet chat sessions on the first Monday of each month: each session has a theme and internet

¹⁷⁶ <http://www.orphanet-france.fr/national/FR-FR/index/page-d-accueil/?lng=FR>

users can ask the team questions 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 are collected by means of qualitative and quantitative surveys targeting users of the information and support service.

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

Other sources of information on rare diseases

The French Agency for the Sanitary Security of Health Products (*Agence Française de Sécurité Sanitaire des Produits de Santé* – AFSSAPS¹⁷⁷) 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.

Since June 2006, the French General Directorate for Health (*Direction Générale de la Santé* - DGS) in the French Ministry of Health has produced health care and information cards for the rare disease patients, in close collaboration with health professionals and patient organisations, within the scope of the first French National Plan for Rare Diseases. These cards are distributed by health professionals treating the patients concerned. They provide information for health professionals about the patient and gives the patient brief information on his/her disease. Within the second plan, a new model of card for patients will be produced.

In 2009, the French Minister for Health relaunched the Personal Medical Record (DMP) project. The actual deployment will start in 2012, after building of infrastructures and services in 2010-2011. This facultative digital record, which will concern rare disease patients (as it is primarily aimed at patients with a chronic illness), should improve the quality of coordination of treatment for both patients and health professionals, and help information exchange.

In 2010, the site www.droitsdesmalades.fr, which informs all citizens about their healthcare rights, was launched. In addition, the patient organisation Sparadrap¹⁷⁸ 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.

Good practice guidelines

Since the beginning of the first national plan, the Reference Centres produced 45 national good practice guidelines (PNDS) for diagnosis, treatment and follow-up of patients with rare disease. These guidelines are published on Orphanet, HAS¹⁷⁹ and Reference Centre websites.

The HAS published clinical practice guidelines¹⁸⁰ for the follow-up of children with deafness under the age of six and their family.

Concerning rare tumours, two national good practice clinical guidelines were published respectively in 2009 and 2010 concerning surgical practices in digestive neoplasia, including peritoneal pseudomyxoma, and gestational trophoblastic disease.

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 a Summer School in Paris: this offers the possibility to train in myology via a condensed 10-day course.

National rare disease events 2011

Each year in December, an annual *Téléthon* is organised by the AFM (*Association française contre les myopathies*) over 30 hours: around €100 million are raised annually during this campaign. The funds raised go

¹⁷⁷ The AFSSAPS was given a new name and new missions on 1st May 2012, following the law reinforcing the monitoring of safety of drugs and other healthcare products, published in December 2011. : *Agence Nationale de Sécurité des Médicaments et des Produits de Santé* (French National for Medicine and Medical Product Safety Agency) <http://www.ansm.sante.fr/>.

¹⁷⁸ <http://www.sparadrap.org/SPARADRAP>

¹⁷⁹ http://www.has-sante.fr/portail/jcms/c_5237/affections-de-longue-duree?cid=c_5237

¹⁸⁰ http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf

towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. Each year, to coincide with the *Téléthon* organised by the AFM, the *Alliance Maladies Rares*, in association with the *Groupama Fondation pour la santé* and the AFM, organises a Rare Disease March (*Marches des Maladies Rares*) involving patients and patient organisations. The *Téléthon*¹⁸¹ and Rare Disease March¹⁸² aim to raise awareness about rare diseases in addition to the Rare Disease Day which is celebrated each February.

A number of events were organised to mark 2011's Rare Disease Day. Firstly, the 28 February 2011 marked the official publication of the second French National Plan for Rare Diseases which will cover the period 2011-2014. The plan was launched by the Secretary of State for Health, Nora Berra, and the Minister of Higher Education and Research, Valérie Pécresse.

The French Alliance for Rare Diseases and Orphanet joined forces with the high speed train (TGV) network from 26-27 February 2011 to raise awareness of rare diseases: TGV passengers were encouraged to participate in a quiz about rare diseases and to learn more of the issues surrounding these conditions in the buffet coaches of trains between Paris and six major French towns.

On 28 April 2011, *France Television* confirmed their support of the *Téléthon* for another 3 years. The 2011 edition, the 25th anniversary, was aired, for the first time, on all five national channels of the French network to assure 30 uninterrupted hours of coverage.

Every year in June, Orphanet and the *Alliance Maladies Rares* organise jointly a one day meeting for all patient organisations to discuss themes of interest in the field of information and dissemination of good practices. On 30 June 2011 the 12th Forum¹⁸³ was held at the *Groupama Fondation* around the theme "Sharing of health data for better healthcare". Topics discussed include the personal medical record (DMP), and the centralisation of data collected by reference centres.

Eurobiomed organised the conference Rare2011 on 2-4 November 2011 in Montpellier in collaboration with local and national partners both from the public and the private sector. This second conference (the first one was organised in 2009) started with two days dedicated to rare diseases at national level, and finished with one day focused on the European context, organised by the EUCERD. Over 300 participants were present from 19 countries. In particular the measures foreseen by the second French National Plan for Rare Diseases were presented in addition to a number of topics concerning research and development, and access to orphan medicinal products, as well as a discussion on how stakeholders should best work together in the field of rare diseases.

Hosted rare disease events in 2011

Amongst the events in the field of rare diseases hosted in France in 2011 and announced in *OrphaNews Europe* were: CliniGene Network of Excellence: Gene Transfer and Therapy: State of the Art and eChiPS - European Conference on Human iPS (7-9 April 2011, Paris), 4th International Friedreich's Ataxia Scientific Conference (5-7 May 2011, Strasbourg), 4th International Congress of Myology (9-13 May 2011, Lille), 3rd International Symposium on Pheochromocytoma and Paraganglioma (14-17 September 2011, Paris), EurokeratoConus II: 2nd European Congress on Keratoconus (23-24 September 2011, Bordeaux), Tuberos Sclerosis Complex Scientific Day (14 October 2011, Paris), Rare 2011: The Eurobiomed Meetings on Rare Diseases (2-4 November 2011, Montpellier), Genodermatoses in the Mediterranean - Together Against Genodermatoses (13- 15 October 2011, Paris), European Wilson Disease Congress (14-15 November 2011, Paris), Sixth European Workshop on Immune-Mediated Inflammatory Diseases (23-25 November 2011, Nice).

France also hosted the European Advanced Postgraduate Course in Classical and Molecular Cytogenetics, co-organised by the European Cytogeneticists Association and two French Universities, as well as the 32nd Annual Course of Pediatric Dermatology on 26-29 April in Arcachon.

Research activities and E-Rare partnership

National research activities

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) in the French Ministry of Health for clinical research via funding of the PHRC Programme (*Programme*

¹⁸¹ <http://www.afm-telethon.fr/le-telethon/le-telethon-2011>

¹⁸² <http://www.alliance-maladies-rares.org/article/marche-des-maladies-rares-2011-98>

¹⁸³ <http://www.orpha.net/orphacom/cahiers/docs/FR/XIIforum.pdf>

Hospitalier de Recherche Clinique – Hospital Clinical Research Programme) sponsored by National Health Insurance of the French Social Security System;

- the INSERM for translational clinical research.

In addition, some charities and private foundations provide funding for research, such as the AFM. The AFM launched only one out of the two usual annual calls for proposals in 2011.

The articulation between these funding sources should be improved under the second plan to make it easier to apply for funding for rare diseases. The future *Fondation Maladies Rares*, foreseen in the second plan, will participate to research activities for rare diseases.

The *GIS Maladies Rares* (Institute for Rare Diseases) was created in 2002 to coordinate and support research into rare diseases and to initiate and implement research on rare diseases at national and European levels. At national level, the *GIS Maladies Rares* has been instrumental in implementing in the early 2000 research programmes (through yearly calls for research projects) on rare diseases (in particular networks), which have been later on entrusted to the French National Agency for Research (ANR) in the context of the first French National Plan for Rare Diseases (2004-2008). Several targeted strategic actions are carried out by the *GIS Maladies Rares*¹⁸⁴ to facilitate (and fund) access to technology platforms (i.e. genetically modified animal models, high throughput sequencing, drug-screening etc.) for the French community of researchers on rare diseases.

In 2009, different public bodies joined together to create the “*Plateforme Mutation*” that aims to identify unknown mutations in rare diseases by means of high throughput sequencing technology.

In 2010, the Ministry for Higher Education and Research gave the outlines of the Health and Biotechnology programme of the national “grand emprunt” (loan): this scheme aims to invest €8 billion into research, including national and European technological platforms, genotyping, screening and production of stem cells, industrial production of cellular therapies, creation of laboratories for the production of biomedicines, running of clinical trials, acquisition of phenotyping material etc. All of these areas would be beneficial to the field of rare diseases.

In 2010, the AFM allocated a budget of €73 million to research the field of neuromuscular diseases and rare diseases.

In June 2010, Généthon announced¹⁸⁵ the opening of a production unit for vectors for genetic therapies (Généthon Bioprod) in 2011. The production of industrial-sized batches is a step towards clinical trials of genetic therapies for rare diseases.

OrphanDev launched its first newsletter in October 2010: the aim of this network is to increase the number of clinical trials for rare diseases in France and to improve their quality. The network has been formed within the *Centre de Gestion des Essais des Produits de Santé* – CeGEPS (Centre for the Management of Health Product Trials).

According to a report published every two years by the LEEM (French Pharmaceutical Companies Union) on international clinical research, the number of clinical trials carried out in France is diminishing in comparison to other countries. This trend could be explained by factors such as cost, quality and speed, but also factors linked to patients such as the ability to find patients who have never been treated for a certain disease. However, the report notes that a large proportion of trials in phase 1 and 2 are carried out in France, and that France is the best performing country in a number of fields including rare diseases¹⁸⁶.

Other funding opportunities for rare disease research in 2011 included grants and calls launched by the following organisations/institutes: Fédération Nationale d’Aide aux Insuffisants Rénaux, Fondation Groupama, la Fondation de France, Association pour la Recherche sur la Sclérose latérale, Fondation de recherche ELA, National Niemann-Pick Disease Foundation (NNPDF), Universal Biotech, ARTHRITIS Fondation Courtin, Connaître les Syndromes Cérébelleux (CSC), Association Strümpell-Lorrain (ASL-HSP) et Association Française Ataxie de Friedreich (AFAF), Institut de Recherche en Santé Publique (IReSP), Fondation Line Pomaret Delalande, Association Neurofibromatoses et Recklinghausen, Fondation Jérôme Lejeune, ECD Global Alliance, Vaincre la Mucoviscidose, Agence de la biomédecine, NA Advocacy, Genespoir, Association pour l’étude de la pathologie pédiatrique, Retina France etc.

Participation in European projects

France participates, or has participated, in European rare disease research projects including: ARISE, ANTEPRION, ANTIMAL, AUTOROME, BIOMALPAR, BIO-NMD, BRAINCAV, BNE, CARDIOGENET, CAV-4-MPS,

¹⁸⁴ The *GIS Maladies Rares* will join the *Fondation Maladies Rares (FMR)* when the FMR will be set up.

¹⁸⁵ <http://www.genethon.fr/index.php?id=368>

¹⁸⁶ <http://www.leem-media.com/leem/content/download/6775/43352/file/13-01-2011-leem-enquete-attractivite-2010-rapport.pdf>

CUREFXS, CLINIGENE, CONTICANET, CONTICABASE, CHEARTED, CRUMBS IN SIGHT, CUREHLH, CRANIRARE, ELAST-AGE, EDEN, EPOKS, EMINA, ERMION, EVI-GENORET, EPINOSTICS, EUROBFNS, EuroGeBeta, ENRAH, ENS@T-ACC EUNEFRON, EMSA-SG, EUMITOCOMBAT, EURAMY, EUREGENE, EUROCARE-CF, EUROAGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROAS, EURO IRON1, EURO-LAMINOPATHIES, EURORETT, EURO-CDG, EURO-SCAR, EUROSCA, EURSPA, EUROTRAPS, ENCE-PLAN, EUSTAR, EPOKS, EURO-PADNET, EURIOFNET, FAD, GETHERTHAL, GENESKIN, GENOMIT, GENOSTEM, HMA-IRON, HSCR, HEMO-IPS, HAEIII, HUE-MAN, IPF-AE, INHERITANCE, 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, NOVELPID, NEMMYOP, NEUTRONET, NSEuroNet, OSTEOPETR, PODONET, PEMPHIGUS, RARE-G, RATSTREAM, RAPOSDI, RISCA, SKIN-DEV, SKINTHERAPY, STEM-HD, SIOPEN-R-NET, RHORCOD, RDPLATFORM, TB CHINA, TRANSPSMART, THERAPEUSKIN, TUB-GENCODEV, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPath.

E-Rare

The *GIS Maladies Rares* is the coordinating partner of the E-Rare for Research Programmes on Rare Diseases, and organised the first joint transnational call in 2007¹⁸⁷ 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 projects/consortia). France took part in the 2nd E-Rare Joint Transnational Call in 2009 and France 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.

IRDiRC

The AFM (*Association Française contre les myopathies*) and French National Agency for Research (*Agence Nationale de la Recherche*), are committed members of the IRDiRC.

Orphan medicinal products^{188,189}

Four institutions are involved in the field of orphan medicinal products on the French market: the French Agency for the Sanitary Security of Health Products (AFSSAPS, which will become the ANSM¹⁹⁰ in 2012), 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 Companies Union) 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 their 10th annual overview of therapeutic advances with an edition covering 2010¹⁹¹. Thirty-five contributions to the improvement of medical services were noted, especially in the fields of cancer, infection and rare diseases. Five new products were presented in the field of rare diseases: Ilaris, Fibrogammin, Eirfapse, Revolade and Myozyme. Torisel, Gliolan and Afinitor were also cited.

Orphan medicinal product committee

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

¹⁸⁷ http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf

¹⁸⁸ This section has been written using the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)*

¹⁸⁹ 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)*

¹⁹⁰ www.ansm.sante.fr

¹⁹¹ <http://www.leem.org/sites/default/files/Bilan%20des%20avanc%C3%A9es%20th%C3%A9rapeutique%202010.pdf>

Orphan medicinal product incentives

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

Free scientific advice is available for medicines from the AFSSAPS as well as CT authorisation and compassionate use authorisation (cohort ATU) from the AFSSAPS. 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 the expectations of the HTA bodies on the data expected concerning especially the relative effectiveness assessment in usual care.

Sponsors of orphan medicinal products are exempted from taxes to be paid by enterprises promoting pharmaceutical specialities or wholesale distributors under health and social legislation. These taxes are: the tax on the promotion of pharmaceuticals, based on the promotion costs of laboratories; the tax paid by the laboratories for the AFSSAPS; the safeguard clause for medicinal products; the tax on direct sales; the tax on the distribution of medicines. 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.

A report published by the French Economic Committee for Health Products (*Comité Economique des Produits de Santé – CEPS*) on 31 July 2010, cited a study of the evolution of sales of orphan medicinal products and called for a revision of the subventions and benefits accorded to orphan medicinal products which made a turnover equal to, or above, €20 million.

In October 2010, a proposed law to finance the French Social Security system included specific provisions for tax exemptions for orphan medicinal products: the Minister for Health accepted to raise the threshold for tax exonerations to orphan medicinal products, which was initially foreseen to be fixed at €20 million of sales. This threshold will now be raised to orphan medicinal products making a turnover equal to, or above, €30-40 million.

The public authorities have also evoked in 2010 abrogating the framework agreements which exempt orphan medicinal products from certain regulations, and for orphan medicinal products costing more than €50 000 per year and per patient that the revenue and international pricing be capped. An obligation to treat all patients concerned 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 an opinion about the actual benefit that defines the pertinence of reimbursement and the level of copayment, and specifies the clinical added value of the drug that assesses the relative effectiveness and is the basis for price definition. For innovative drugs (new therapeutic modality, efficacy and tolerance presumably good, 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 rapidly after MA is granted. 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.

Orphan medicinal product market availability situation

According to the registry of the French Agency for the Sanitary Security of Health Products (AFSSAPS) 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: Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyf, Firdapse, Flinsit, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren,

Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Photobarr, Prialt, Replagal, Revatio, Revlimid, Revolade, Rilonacept Regeneron, Savene, Siklos, Soliris, Somavert, Sprycel, Tassigna, Thalidomide Celgene, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Vpriv, Wilzin, Xagrid, Yondelis, Zavesca.

- Orphan medicinal products with valid market authorisation without mention of commercialisation: Ceplene, Esbriet, Mepact, Peyona, Plenadren, Tobi Podhaler, Votubia, Vyndaqel.

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)* 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. Orphan medicinal products intended for ambulatory use and that have a very low target populations are generally made available through this retrocession process¹⁹².

Within the 62 orphan medicinal products that have been granted MA in Europe, all but one 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*¹⁹³, "*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 obligatory for the first prescription for an orphan medicinal product to be validated by a Reference Centre designated for the patient's rare disease when available, or by the Competence Centre directly linked to the Reference Centre.

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 pharmaceutical products and of non-covered medical devices or services by the National Health Insurance¹⁹⁴. Pharmaceutical products (orphan or non-orphan medicinal products) used off-label, medical devices or services intended for rare diseases are in particular concerned. The coverage is allowed for a limited renewable period by the French Ministry of Health after the HAS has given a positive advice or a recommendation; concerning drugs, the HAS has to ask for the advice of the AFSSAPS before giving its own recommendation. This process will be modified in 2012 further the law reinforcing the monitoring of safety of drugs and other healthcare products, published in December 2011.

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 AFSSAPS. 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* (Temporary Authorisation for Use) from the AFSSAPS if there is a public health need. The drug must fulfil the following criteria: the drug must treat a serious or rare disease; no therapeutic alternative to the drug should be available; the drug must have a positive risk/benefit and the patient cannot be treated within a clinical trial. The aspect of the drug (quality, security and efficacy) and the medical environment (disease and alternatives) are evaluated before receiving the *ATU*. Protocols for therapeutic use and information collecting are mandatory for cohort *ATU* and optional for nominative *ATU*.

The AFSSAPS gave in its 2009 activity report¹⁹⁵, published in 2010, an overview of the *ATU* and of the *Plans d'Investigations Pédiatriques* (Paediatric Investigation Plans - PIP): these two areas concern the field of rare diseases and orphan medicinal products. In 2009, for the 9 orphan medicinal products with a new European MA, 6 were already available within the *ATU* system.

¹⁹² *EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, C. Hahl, F. Bachner (2011) pp. 49-50.

¹⁹³ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*. 2005 Revision (p14)

¹⁹⁴ Article L162-17-2-1 of the Social Security Legal Code.

¹⁹⁵ http://www.afssaps.fr/var/afssaps_site/storage/original/application/a40deaca3add3f9e767493ab831897e0.pdf

Temporary Treatment Protocols (*Protocoles temporaires de traitement*) can 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.

The new law reinforcing the monitoring of safety of drugs and other healthcare products, published on 29 December 2011, 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*.

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

Orphan devices

No specific information reported.

Specialised social services

Respite care services are available for patients whose care is demanding on behalf 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 centres (*Centres communaux d'action social* - 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 budgets or patient organisations. The AFM has a number of administrative, medical and social coordinators who assist families with their specialised 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. GERMANY¹⁹⁶

Definition of a rare disease

Stakeholders in Germany accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no 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

¹⁹⁶ 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.

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)¹⁹⁷ – 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 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.

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).

Hospitals next to outpatient physicians are entitled to provide outpatient care for rare diseases patients if they have received prior authorisation by the competent Land authority (Social Code V, Section 116b): however this applies only to certain rare diseases according to a list which has been stipulated by law (Social Code V, Section 116b). The Federal Joint Committee (*Gemeinsamer Bundesausschuss, G-BA*) can extend this list. 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 Germany. 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 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*). 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 hospitals as well as the cross-institutional measures for quality assurance. In this context, for the purpose of ensuring the quality of treatment, the *G-BA* may also lay down certain minimum numbers of patients treated per year in a certain ‘Section 116b centre’.

¹⁹⁷ <http://namse.de/>

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.

Legislation provides the basis for the contracting of *Ambulante Spezialfachärztliche Versorgung* (highly specialised care) for a limited number of diseases (see above), some of which are rare.

There are already several self-appointed centres for rare diseases in Germany. 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 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.

Pilot European Reference Networks

German teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN-CF (main partner), ENERCA, EPI, EPNET, EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma Network (main partner), PAAIR, EN-RBD and Treat-NMD (Main partner).

Registries

There are some registries for rare diseases in Germany. 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 disorders. 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. Germany contributes to European registries such as EUROCAT, TREAT-NMD, EBAR, EHDN, EIMD, EurIPFnet, E-IMD, EURIPEDES, European Alport registry, EuroDSD, EUROSCA-R, EUTOS, and RegiSCAR.

Genetic testing and Newborn Screening Policy

On 1 February 2010, a law passed by the German Bundestag regulating genetic testing in humans officially came into effect. The Genetic Diagnostics Act (Gen DG) regulates the practice of testing on humans as well as the handling of samples and data but does not extend to testing and data/samples undertaken for research purposes. Notably, the legislation prohibits prenatal testing for diseases that typically have onset after the age of adulthood (age 18). All persons undergoing genetic testing for medical purposes must be offered counselling before and after testing. The scope of the regulation includes predictive, prenatal and postnatal genetic testing. The Act seeks to reduce discrimination and to enhance the quality of testing in Germany.

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 1449 genes and an estimated 1479 diseases in the Orphanet database¹⁹⁸.

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 live of people living with a rare disease. ACHSE is an active member of EURORDIS and a member of its Council of National Alliances.

¹⁹⁸ Information extracted from the Orphanet database (September 2011), no verification by the German Federal Ministry of Health.

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 means 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 deals 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 German¹⁹⁹ 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 launched²⁰⁰. This German language page is maintained by the Orphanet-Germany team and features information, news and events specific to field of rare diseases in 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)²⁰¹ ensuring public access to package leaflet, summary of product characteristics (Fachinformation in Germany) and the assessment report (publicly accessible version).

On 1 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 a public database run by DIMDI.

The ACHSE website²⁰² 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 KINDERNETZWERK²⁰³ 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

¹⁹⁹ www.orphanet.de

²⁰⁰ <http://www.orpha.net/national/DE-DE/index/startseite/>

²⁰¹ <http://www.dimdi.de/static/de/amg/pharmnet/index.htm>

²⁰² www.achse.info

²⁰³ www.Kindernetzwerk.de

website²⁰⁴ (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 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?”²⁰⁵.

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.

National rare disease events in 2011

The German Society of Human Genetics (GfH) holds an annual conference (Regensburg, 16-18 March 2011) 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.

A number of actions and events were organised to mark Rare Disease Day 2011 in Germany. Events were organised by ACHSE members with support and coordination of ACHSE in 11 German cities: Bad Oeynhausen, Berlin, Dessau, Essen, Hamburg, Hannover, Cologne, Magdeburg, Stuttgart, Würzburg. People from different rare disease patient organisations teamed up to organise different events. In Dessau, Magdeburg and Cologne there were events in the hospitals organised by the hospitals' staff. This day provided the opportunity to raise awareness, and to inform public about the problems and needs of people living with rare diseases. As in the previous year, at all the events hundreds of red ACHSE-balloons were released to rise into to sky. Apart from these awareness events the Eva Luise and Horst Köhler foundation for people with rare diseases in cooperation with ACHSE awarded another Eva-Luise-Köhler- Award for a research project that has not been realised yet, thus strengthening research for rare diseases.

A short film was produced for the ACHSE-project "Wissenskarawane für die Seltenen" (caravan of knowledge for people with rare diseases) by SympathieFilm which was financed by the statutory health insurance funds Barmer GEK, TK, DAK, KKH, HEK.

On 26 February the 2nd Rare Disease Day Symposium was organised by Orphanet at the Medical School of Hanover. This event was well attended by 36 different support groups taking part by presenting

²⁰⁴ www.nakos.de

²⁰⁵ https://www.iqwig.de/download/V10-01_Executive_Summary_Evidence_for_guidelines_on_rare_diseases.pdf

information booths to the public. The motto of Rare Disease Day “rare but equal” was reflected by 8 interesting talks from experts presenting different aspects of the actual health care situation for patients with rare diseases in Germany. Different structures were highlighted, including a report of experiences of the first official centre for rare diseases in Germany during its first year of existence. The audience also learned about the structure of different networks and their impact on patient care, the latest developments in the field of orphan medicinal products and how to improve quality of specialised centres by certifying them. About 250 people visited this event. The press also attended the meeting, with the local print media publishing a report on this day, along with reports on television of the Symposium.

A symposium on rare diseases was held at the Heidelberg University Hospital on 15 April 2011. The event was well attended and several support groups took part in the meeting by presenting information booths to the public. Talks covered different topics in the field of rare diseases were given by representatives of associations and of the German Parliament, clinicians and researchers as well as a round table discussion with people living with a rare disease and clinicians was presented. The topics included: health policy, the latest scientific developments on rare diseases and the role of networks to improve the care of rare disease patients. The event was reported on in the local print media and on television.

Rare diseases were also one of the topics of the Year of Science 2011 – Research for Our Health – which was organised by the Federal Ministry of Education and Research (BMBF) in collaboration with Wissenschaft im Dialog (WiD) - an initiative by the German Science - and numerous partners from different fields such as science, industry, politics and culture. One of the events was a photo exhibition titled “Orphans of Medicine – Living with a rare disease” which was hosted in Munich June 29 to July 22 2011. The exhibition was organised by ACHSE and funded by the BMBF. In addition, rare diseases were one of the topics presented in the exhibition titled "Discoveries" on the island of Mainau from 20 May to 4 September 2011.

A meeting of the networks for rare diseases funded by the German Federal Ministry for Education and Research (BMBF) was held on 20 September 2011 in Munich. The participants included representatives of the funded networks, PT-DLR (Project Management Organization at the DLR, acting on behalf of the BMBF) and ACHSE.

Hosted rare disease events in 2011

Amongst the rare diseases events hosted by Germany and announced in OrphaNews Europe were: 3rd International Adrenal Cancer Symposium: From Molecular Pathogenesis to Clinical Outcome (17-19 February 2011, Würzburg), Fourth Berlin Conference on IP in Life Sciences: Rare Diseases – Blockbusters in the Niche (18 February 2011, Berlin), 3rd Symposium on Disorders of Sex Development (20-22 May 2011, Lubeck), The World Orphan Drug Summit (31 May – 1 June 2011, Frankfurt), International Conference on Inherited Disorders of Muco-Ciliary Clearance (Focus on PCD) (20-22 May 2011, Muenster), 2011 International Expert Meeting: Large Congenital Melanocytic Nevi/Neurocutaneous Melanocytosis (6-7 May 2011, Tuebingen, Germany), 15th International Workshop on Fragile X and Early-Onset Cognitive Disorders (4-7 September 2011, Berlin), 1st CURE-Net International Conference for Congenital Uro-Rectal Malformations (21-22 October, Heidelberg).

In addition to these events, the 4th International Postgraduate Course on Lysosomal Storage Disorders: Diagnostic Background and Clinical Therapy took place at the University of Rostock in Berlin from 14-15 November 2011.

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.

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: AUTOROME, ANTEPRION, BIOMALPAR, BNE, CAV-4-MPS, CRANIRARE, CURE-FXS, CHD PLATFORM, CILMALVAC, CUREHLH, EDEN, EMVDA, ENRAH, ENCE-PLAN, EURADRENAL, EUCILIA, EUNEFRON, EURIPFNET, EUROBONET, EUROBFNS, EURODS, EURO-CDG, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROSCA, EURO-SCAR, EUROTRAPS, EURORETT, EUROSPA, ERMION, EuPAPNet, EUBNFS, EURO-CGD, ELA2-CN, EMINA, EPINOSTICS, EUREGENE, EUROPEAN LEUKEMIA NET, EMSA-SG, ESDN, FASTEST-TB, GETHERTHAL, GENOMIT, HMA-IRON, HAE III, HDLOMICS, HUE-MAN, HMANASP, IPF-AE, INTHER, KINDLERNET, LEISHDRUG, MANASP, MITOTARGET, MTMpathies2, MYORES, MIMOVAX, MOLDIAG-PACA, NEUROSIS, NSEuroNet, NEUTRONET, NEMMYOP, NEWTBDRUGS, PULMOTENSION, OVCAD, OSTEOPETR, PODONET, PEMPHIGUS, RD PLATFORM, RevertantEB, RHORCOD, RATSTREAM, RARE-G, RISCA, SKIN-DEV, TRANSPSMART, 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.

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 company²⁰⁶. See further under chapter “Orphan medicinal product reimbursement policy”.

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

²⁰⁶ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011)

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 Euros 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 effects²⁰⁷.

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 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 website²⁰⁸. Once authorised, all orphan medicinal products are fully reimbursed by statutory health insurance.

Orphan devices

No specific information reported.

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.

Clinician stakeholders, for the precise evaluation of the burden of a RD on public health, propose the use of supplementary indices such as the annual rate of births of affected new-borns 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.

²⁰⁷ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011)

²⁰⁸ www.bfarm.de

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 2008-2012²⁰⁹) 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 Diseases²¹⁰ co-organised by the Greek Alliance for Rare Diseases (PESPA) and EURORDIS, was held 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 Greek.

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.

In fact, most of the objectives of the proposed nation 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) jointly to those of common diseases.

In 2010 the new Scientific Committee for Rare Diseases appointed by KEELPNO organised (with minimum funding) a program to evaluate the implementation and efficacy of the main strategic priorities defined in the scope of the Europlan project that are incorporated in the Greek NHS. The program started in 2011 with the following main objectives: i) to identify the expertise centres (CEs) involved in the care of patients with rare diseases, describe their structures and activities, evaluate the quality of health services they provide; ii) to investigate measures to upgrade the quality of the provided care; and iii) to introduce applicable strategies defined by Europlan, which are not included in the activities of expertise centres. Preliminary data from the survey are reported.

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

²⁰⁹ http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf

²¹⁰ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report%20Gre%20EUROPLAN%202010.pdf (accessed 28/01/2011)

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 a 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.

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:

- Thalassaemia: 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 following 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 national Thalassaemia Prenatal Diagnosis Centre covering 60-70% of prenatal diagnosis of thalassemia.
- 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.

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.

Pilot European Reference Networks

Greece participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, EUROHISTIONET, EN-RBD and TAG.

Registries

There is currently no national registry for rare diseases in Greece. One of the main tasks of the new Scientific Committee, mainly consisting of clinicians caring for patients with rare diseases, is to set up a national registry, according to the international standards.

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 immunodeficiencies.

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 policy of neonatal screening was not further developed in 2011 in the Greek NHS.

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 covering centres of expertise are official reference laboratories and fulfil European guidelines.

Diagnostic tests are registered as available in Greece for 104 genes and an estimated 160 diseases in the Orphanet database²¹¹.

National alliances of patient organisations and patient representation

PESPA (the Greek Alliance for Rare Diseases) 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.

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 relative 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 and expert units. (i.e., ELPIDA donated to “Aghia Sophia” Children’s Hospital a modern and well-equipped Unit, “The Paediatric Oncology Unit. Marianna Vardinoyiannis –ELPIDA”, for the multidisciplinary care of children and adolescents with cancer: the Unit with a capacity of 126 beds started operating in January 2011).

There are currently no public funding schemes to support 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’s Department of Genetics (from 2009). 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 allocated the amount of €50’000 for the translation of the rare disease encyclopedia for experts in the Orphanet website in Greek. The Orphanet Greece national website in Greek was launched in 2011²¹².

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 help line for rare disease information in Greece; some services, mainly voluntarily are offered by PESPA members who provide psychological support and general information.

²¹¹ Information extracted from the Orphanet database (September 2011).

²¹² <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 PESPA website offers 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 2011

National rare disease events are either events for the patients and the public to disseminate basic information on clinical signs and treatment of rare diseases or scientific events addressed to expert physicians and scientists.

The National Association of Rare Diseases (PESPA) announced Rare Disease Day 2011, which was held under the auspices of President of the Republic Karolos Papoulias. A speech was given by Professor of Cancer Prevention and Professor of Epidemiology at the University of Harvard, Mr. Dimitrios Trichopoulos, Member of the Greek Academy of Sciences, and a retrospective exhibition of paintings by Katerina Lambrou, at the Cultural Center of Athens with donations going to the National Association of Rare Disorders and the Greek Society of Tuberous Sclerosis. PESPA organised a national conference on “Autoimmune Diseases: Today and Tomorrow” on 25-26 November 2011.

Events related to rare diseases are organised by most of the national patients organisations on the day devoted to the particular disease. National patient organisations organised during 2011 their annual meetings, conferences or congresses and discussed with specialists the recent advances in management and other topics related to the interest of the societies.

A considerable number of educational events on rare diseases aimed at physicians and the scientific community are organised each year by university departments, research institutes, expertise centres and scientific speciality societies in the form of meetings, workshops, lectures, training courses etc. Scientific events are usually focused on a single rare diseases or a number of homogeneous rare diseases.

For the more interesting educational events, proceedings are published.

Sponsorship for these events comes mainly by pharmaceutical companies and occasionally from patient organisations

Hosted rare disease events in 2011

No rare disease related events hosted by Greece were announced in *OrphaNews Europe* in 2011.

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, EUROPEAN LEUKEMIA NET, EVI-GENORET, GEN2PHEN, GETHERTHAL, HDLomics, IPF-AE, ITHANET, MYASTAID, NEUROPRION and TRANSPOSMART.

E-Rare

Greece, through the General Secretariat for Research and Technology (GSRT), participated in the 2nd Joint Call of E-Rare-1. In this context, one project coordinated by a Greek team (with a total funding of around €140,000) 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.

IRDIRC

Greek funding agencies are not currently committed members of the IRDiRC. Nevertheless the possibility to join IRDiRC through E-Rare-2 is under consideration.

Orphan medicinal products

The Greek National Organisation for Medicines (EOF²¹³) 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.

Orphan medicinal product committee

No specific information reported.

Orphan medicinal product incentives

No specific information reported.

Orphan medicinal product market availability situation

The following orphan medicinal products are available in Greece: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Celpen, Cystadene, Diacomit, Elapraxe, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyne, Firdase, Flioland, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Onseno, Orfadin, Pedeia, Peyona, PhotoBarrl, Prialt, Replagal, Revatio, Revlimid, Revolade, RInoccept, Regeneron, Savene, Siklos, Soliris, Somavert, Sprycel, Tepadina, Tassigna, Thalidomide, Celgene, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Yondelis, Zavesca. Of the orphan medicinal products authorised by the EMA, 42 are readily available on the Greek market, whereas 11 more are imported by the Greek Institute of Pharmaceutical Research and Technology. The remaining 8 OD could be imported on request by the Greek Institute of Pharmaceutical Research and Technology.

Orphan medicinal product pricing policy

No specific information reported.

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*²¹⁴), 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.

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

²¹³ <http://www.eof.gr>

²¹⁴ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

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.

The NRDC network 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 these indicators;
- It defines public health indicators for rare diseases;
- It initiates the elaboration of rare diseases 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 efficacy of the rare diseases screening programs;
- It facilitates the rare diseases research projects, the international co-operations;
- It contributes to the development of collaboration between governmental bodies, 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. The Ministry is designating 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, National Public Health Institute, 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 new National Institute for Quality and Organisational Development in Healthcare and Medicines (GYEMSZI). Project based collaboration has been established with universities' internal rare disease coordination units, sociological centres (for studying sociological characteristics of the patient groups), the National Foundation for Disabled Persons (multi-sector conference organisation), 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 diseases²¹⁵, 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. The second Hungarian Europlan Conference on Rare Diseases²¹⁶ (16-17 November 2011) was organised by HUFERDIS, together with the Ministry of National Resources, in Budapest, without European grant support. All stakeholders were present during the two day conference aimed at defining further concrete steps to develop a national action plan for rare diseases.

In 2011, the Ministry of Health appointed a National Coordinator and the National Plan Organising Committee (including the advisory board of the National Rare Diseases Centre and the patient groups) started to develop the National Plan with his leadership to develop a rare disease plan and to elaborate the plan. 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 will be sought by the end of March 2012, and it is hoped by end of June 2012 the plan will be ready to be included in the negotiations of the national budget at the start of August 2012.

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, Pécs 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 various 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 needs to be examined.

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 2012.

²¹⁵ [http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final_report_%20hungary_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_%20hungary_europlan.pdf)

²¹⁶ <http://europlan.rirosz.hu/>

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.

Pilot European Reference Networks

Hungary participates, or has participated, in the following European Reference Networks for rare diseases: EPNET/EPI and Care-NMD.

Registries

The National Register of Congenital Anomalies (VRONY) operates country according to the EUROCAT protocol. The OSZMK 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 and EUROCARE 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.

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 database²¹⁷.

National alliances of patient organisations and patient representation

The Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS) is the national alliance of 38 rare disease patient organisations in Hungary, affiliated with EURORDIS. HUFERDIS is currently encouraging the creation of a Hungarian Rehabilitation Centre for Rare Disease Patients. HUFERDIS represents rare diseases patients in the Hungarian Expert Committee of Rare Diseases (transforming to 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 National Civil Fund 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.

²¹⁷ Information extracted from the Orphanet database (September 2011).

Following a collaboration established between HUFERDIS, NRDC and the Hungarian Orphanet team, the EURORDISCare 2 and 3 surveys were carried out in Hungary. HUFERDIS takes part in the several international projects including Europlan, POLKA, BURQOL-RD, Rare Disease Days, 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. Hungary won the POLKA competition of EU Member states with the management of HUFERDIS.

Sources of information on rare diseases and national help lines

Orphanet activities in Hungary

Since 2004 there is a dedicated Orphanet team in Hungary, currently hosted by the University of Pécs. 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.

Official information centre for rare diseases

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

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), which was renovated during 2011. 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 (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 organises since 2009 a 3-day clinical genetics course covering among others the diagnosis and management of selected rare diseases; the meeting designated for specialists in the field as well as for family practitioners. 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 2011

HUFERDIS, the Hungarian rare disease alliance, organised the Hungarian Rare Disease Day as an informal central event of the EU supported by the Hungarian presidency²¹⁸ on 26 of February 2011 in Budapest. The event was attended by a range of stakeholders from Hungary and Europe and gave insights into actions at Hungarian and European level in the field of rare diseases. Many parallel programmes were organised: an 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. During the day Dr. Ildikó Horváth, Head of Department for Health Politics, State Secretariat for Healthcare, Ministry of National Resources, and her colleague Ildiko Szy presented the enacted clinical guidelines for rare diseases. More than 800 people, several journalists and TV teams participated at the event. Many interviews were given. These all guarantee that awareness about rare diseases is developing continuously.

The Orphanet Hungary team and the NRDC are also involved in Rare Disease Day events organised by HUFERDIS.

The second Hungarian Europlan Conference on Rare Diseases²¹⁹ (16-17 November 2011) was organised by HUFERDIS, together with the Ministry of National Resources, in Budapest, without European grant support. All stakeholders were present during the two day conference aimed at defining further concrete steps to develop a national action plan for rare diseases. 125 participants took part in the two day event including experts, patients and representatives of government and the Industry. Participants at the conference monitored a number of main priorities: the creation of a Committee to lead the development of a national plan, the accreditation of centres of expertise for rare diseases, the inclusion of rare diseases in health care and social care systems (currently under reorganisation), the organisation of external quality control of accredited institutions, the provision of information on rare diseases in Hungarian, the participation of Hungary in EU projects, the organisation of awareness campaigns, and the organisation of a body to maintain a rare disease information helpline.

Other events included a “Prenatal Diagnosis of Down Syndrome: How Best to Deliver the News” was organised in Debrecen by the local patient organisations, the Debrecen University’s departments and the NRDC. A working group meeting was held in Budapest for the partners involved in the audit for the prenatal screening and diagnosis of Down syndrome organised by NRDC and VRONY. A symposium on “Multidisciplinary care for Rare Disease” was organised in Pecs by the National Rare Disease Research Coordinating Centre and NRDC.

Hosted rare disease events in 2011

The Rare Disease Day of 2011 became the official event of the Hungarian Presidency of the European Union, after the initiation of HUFERDIS. Several European experts gave presentations with simultaneous Hungarian/English translation and live online broadcasting of the conference on the internet, organised by HUFERDIS. The opening speech was given by prof. Dr. Miklós Réthelyi, Hungarian Minister of National Resources.

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 (2004-2006) €3 million went to support research grants. The summary report of the 2009-2011 program evaluation will be available in 2012. 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 periconceptual folate status and on attitude towards different supplement programs).

²¹⁸ <http://sites.rirosz.hu/rbv/ritka-nap-2011/programme-in-english>

²¹⁹ <http://europlan.rirosz.hu/euroterv-ii-konferencia-1/az-elhangzott-eloadasok>

A multidisciplinary centre had been established in the Semmelweis University (Budapest) on the rare neurological 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 program²²⁰.

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 Pécs. 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. The new 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.

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 will be 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, EUROBONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, NMD-CHIP, TREAT-NMD, SCRIN-SILICO, 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.

IRDiRC

Hungarian funding agencies are not currently committed members of the IRDiRC.

Orphan medicinal products²²¹

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

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 lizinát (inhalációs alkalmazásra), Ceplene™ (Hisztamin-dihidroklorid), Cystadane™ (Betaine anhydrous), Diacomit™ (stiripentol) , Dudopa™ (Levodopa/Carbidopa (Gastroenterális alkalmazás)), Elapraxe™ (iduronate-2-sulfatase) , Evoltra™ (clofarabine)

²²⁰ <http://www.molneur.eoldal.hu/cikkek/english>

²²¹ 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)

, Exjade™ (deferasirox), Fabrazyme™ (α-Galactosidase A), Firazyr™ (icatibant acetate), Firdapse™ (amifampridine), Gliolan™ (5-aminolevulinic acid hydrochloride), Glivec™ (Imatinib mesilate), Ilaris™ (Az IgG1/K osztályba tartozó humán IL 1β elleni rekombináns humán monoklonális antitest), Increlex™ (Mecasermin rinfabát), Inovelon™ (Rufinamid), Ixiaro™ (Tiszított, inaktivált japán encephalitis SA14-4-2 vírus vakcina), Kuvan™ (Tetrahydrobiopterin), Litak™ (cladribine), Lysodren™ (mitotane), Mepact™ (Muramil Tripeptid Foszfátidil Etanolamin), Mozobil™ (plerixafor), Myozyme™ (Recombinant human acid α-glucosidase), Naglazyme™ (N-acetilgalaktózamin-4-szulfatáz), Nexavar™ (Sorafenib tosylate), Nexavar™ (sorafenib tosylate), Nplate™ (Rekombináns megakaryocita képződést serkentő fehérje), Nymusa™ (caffeine citrate), Onsenal™ (Celecoxib), Orfadin™ (Nitisinone), Pedea™ (Ibuprofen), Photobarr™ (Porfimerum nátrium(fotodinámias kezeléscéljára), Prialta™ (α-Galactosidase A), Replagal™ (α-Galactosidase A), Revatio™ (Sildenafil citrate), Revlimid™ (Lenalidomid), Revolade™ (Eltrombopag olamin), Savene™ (Dexrazoxane), Siklos™ (Hydroxyurea), Soliris™ (Eculizumab), Somavert™ (pegvisomant), Sprycel™ (Dasatinib), Tasigna™ (Nilotinib), Tasigna™ (Nilotinib), Tepadina™ (Thiotepa), Thalidomide Celgene™ (Thalidomide), Thelin™ (Sitaxentan nátrium), Torisel™ (temsirolimus), Torisel™ (Temsirolium), Tracleer™ (Bosentan), Tracleer™ (Bosentan), Trisenox™ (Arsenic trioxide), Ventavis™ (Iloprost), Vidaza™ (Azacitidin), Vidaza™ (azacitidine), Volibris™ (Ambrisentan), Votrient (Patorma)™ (Pazopanib hidroklorid), Wilzin™ (Zinc acetate dihydrate), Xagrid™ (Anagrelide Hydrochloride), Yondelis™ (Ecteinascidin 743), Yondelis™ (Trabectedin), Zavesca™ (miglustat), Zavesca™ (Miglustát).

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*²²², "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"²²³. 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.

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.

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.

²²² *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)*

²²³ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)*

HUFERDIS joined the therapeutic recreational programs of a member association (Hungarian Williams Syndrome Association) and organised programmes for capacity building and training, networking, awareness raising, exchange of information and best practices, during a special development family camp and after.

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 Diseases²²⁴ 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 first steps have been taken to elaborate a plan. 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 in the second half of 2012. A national consultation on the national plan and second national conference on rare diseases are planned for 2012.

Centres of expertise

The Health Service Executive (HSE) does recognise that particular centres have particular expertise, and would give specific funds to support those specialist services. The HSE is responsible for these services and supports centres of expertise and laboratories, including 8 cancer centres, the National Centre for Medical Genetics which provides a service for patients (both adults and children) affected by or at risk of a genetic disorder, and 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.

A policy concerning centres of expertise is under development as part of the national plan for rare diseases.

Pilot European Reference Networks

Ireland participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET, EPI, Care-NMD, EN-RBD and the Paediatric Hodgkin Lymphoma Network.

Registries

There are 9 patient registries for rare diseases registered with Orphanet: four of these contribute to the EUROCAT registry. 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

²²⁴ <http://www.europlan.ie/> and http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_ireland.pdf

entitled “Towards a National Strategy for Patient Registries in Ireland, considerations for Government²²⁵” 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 Quality Authority; and the Health Information Bill. The Health Information Bill is expected to be published in 2012 and will address ethical and legal issues concerning data collection and sharing patient data.

Ireland also contributes to other European registries, such as EURO CARE CF and EURO CAT.

Neonatal screening policy

Neonatal screening is in place for galactosaemia, hypothyroidism, phenylketonuria, homocystinuria and maple syrup urine disease. Neonatal screening for cystic fibrosis started as of 1 July 2011²²⁶. New governance arrangements are being developed for screening.

Genetic testing

Genetic testing in the Republic of Ireland is available through the National Centre for Medical Genetics (NCMG)²²⁷, 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 funded via Our Lady’s Children’s Hospital, Crumlin, which in turn is funded by the Irish Health Service Executive. 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 19 genes and an estimated 21 diseases in the Orphanet database²²⁸.

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.

National alliances of patient organisations and patient representation

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 in 1988 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.

In 2011, GRDO, together with the Medical Research Charities Group (MRCG) and the Irish Platform for Patients’ Organisations, Science and Industry (IPPOSI) and other patient organisations grouped together to form the Rare Diseases Towards 2013 Task Force which will support this National Steering Group charged with the development of a national plan for rare diseases and provide input from the appropriate stakeholders. 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 will be used to assist the Taskforce to engage with the Rare Diseases Steering Committee of the Department of Health.

The Irish Platform for Patients’ Organisations, Science and Industry (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

²²⁵ <http://ipposi.ie/index.php/information-centre/patient-registries/179-towards-a-national-strategy-for-patients-registries-report>

²²⁶ <http://www.hse.ie/eng/services/healthpromotion/newbornscreening/>

²²⁷ <http://www.genetics.ie/>

²²⁸ Information extracted from the Orphanet database (September 2011).

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.

Sources of information on rare diseases and national help lines

Orphanet activities in Ireland

Since 2004, there is a dedicated Orphanet team for Ireland and the UK, hosted by the University of Manchester in the UK. 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 Ireland and the UK for entry into the Orphanet database. There is also an Orphanet Ireland national website²²⁹. Under the establishment of the National Steering Group, it is hoped that a plan can be developed to run an Orphanet team for Ireland in an accredited centre in this country.

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

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. IPPOSI provides web-based information and policy support to patient groups. Irish Platform for Patients' Organisations, Science and Industry (IPPOSI) and MRCG are funded partly by the government and membership fees.

In 2008 a report 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 entitled *An investigation into the social support needs of families who experience rare disorders on the island of Ireland*, was published by Rehab Care, a unit of the independent non-profit organisation Rehab Group²³⁰. Amongst the findings, were that 73% of general physicians admit to difficulties in providing patients and families with appropriate information; some 60% of physicians access rare disease information via the internet; and patients need a reliable resource that does not present a worst-case scenario leading to additional stress and worry. The report recommends 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 Family²³¹.

Good practice guidelines

Clinical guidelines exist for certain diseases.

Training and education initiatives

In 2011 IPPOSI and the School of Medicine 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 lecturers on this module are scientists, clinicians and patients

²²⁹ <http://www.orpha.net/national/IE-EN/index/homepage/>

²³⁰ <http://www.rehab.ie/index.aspx>

²³¹ <http://www.cafamily.org.uk/index.php?section=861>

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 2011

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.

On 20 January 2011, the Irish Europlan conference in Dublin took place. The organising committee included members of GRDO (The Genetic and Rare Disease Organisation), IPPOSI, the Irish Platform for Patient Organisations, Science and Industry and the MRCG, the Medical Research Charities Group, Fighting Blindness, Muscular Dystrophy Ireland, EURORDIS, Genzyme Ireland, the National Centre for Inherited Metabolic Disorders, the National Centre for Medical Genetics and the University College of Dublin. The Europlan conference provided a wide range of views from the academic, clinical, private and patient organisation sectors under the topics "Centres of Expertise", "Orphan Drugs and Access to Treatment", "Research" and "Patient Empowerment and Support".

GRDO hosted an information/patient-focused discussion event on Monday 28 February to mark International Rare Disease Day 2011. Those present included people with rare conditions, patient advocates, scientists and clinicians. Topics address included Genetic Testing and Genetic Counselling, Orphan Drugs, Pre-implantation and Genetic Diagnosis.

Hosted rare disease events in 2011

Amongst the events hosted by Ireland in the field of rare diseases and announced by OrphaNews Europe where: The 40th ESPC Symposium on Clinical Pharmacy, which included a Workshop on Cross-Border Healthcare and Rare Diseases (19-21 October 2011, Dublin).

Research activities and E-Rare partnership

National research activities

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, 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 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"²³².

Participation in European research projects

Ireland contributes, or has contributed, in European rare disease research projects including: AUTOROME, EPOKS, EURAPS, EUROPEAN LEUKEMIA NET, EVI-GENORET, GENESKIN, MANASP, MOLDIAG-PACA, NEUROPRION and NOVSEC-TB.

E-Rare

Ireland is not currently a partner of the E-Rare project.

IRDIRC

Irish funding agencies are not currently committed members of the IRDiRC.

²³²IPPOSI Information Document on Rare Diseases – 19 February 2009
<http://www.ipposi.ie/index.php/information-centre/rare-diseases>

Orphan medicinal products

Orphan medicinal product committee

This will be addressed as part of the work of the National Rare Disease Steering Group 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.

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 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 Schemes”.

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 basis²³³.

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, and a waiver for medical care cost, diagnostic work up and therapy for patients with a suspicion, or

²³³ *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 and official identification of Reference Centres for diseases not included in the list. The act that updates the LEAs, recently 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 109 additional diseases, but also a new list of procedures (for example, laboratory assays for the diagnosis of metabolic diseases).

A Committee ensures the interregional coordination for rare diseases between the Ministry of Health, *Istituto Superiore di Sanità* (ISS – the Italian 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 national health care budget and dedicated funds are available for the implementation of regional projects aimed at strengthening the regional service networks (€30 million for 2008 with €5 million for the following years).

In 2008 the National Centre for Rare Diseases (NCRD) 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 NCRD took over the activities carried out for many years by a specific unit within the ISS to tackle rare diseases²³⁴.

In 2009, following an agreement between the Ministry of Health, the NIH and the Italian Regions, €8 million have been 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).

An agreement has been signed between the Government, the Regions and the special statute Provinces of Trento and Bolzano based on the proposal of the Ministry of Labour, Health and Social Policy, concerning guidelines for the correct use of bound resources by the special statute Regions and Provinces, as provided in art. 1, par. 34 and 34bis, Law dated 23 December 1996, n. 662, in order to implement the primary and nationally important objectives for year 2010, including the allotment of €20 million for rare diseases.

On 11-13 November 2010 the Italian Federation for Rare Diseases (UNIAMO F.I.M.R ONLUS), in collaboration with EURORDIS, organised a national conference on rare diseases²³⁵ 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 and 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. By spring 2012 a draft proposal should be ready for stakeholders’ consultation, based on the previous work from 2010 onwards and various stakeholders’ meetings at the Ministry of Health.

As concerns related initiatives, during the 25 May 2011 session of the Permanent Conference for relations between State, Regions and Autonomous Provinces of Trento and Bolzano, an agreement was ratified, formalising the engagement of health authorities in guaranteeing, through concrete actions, the global management and appropriate pathways of health care continuity, which must be homogenous throughout Italy, for patients affected by neuromuscular diseases. This goal was achieved via the intensive work carried out by the Ministerial Conference for Neuromuscular Diseases.

²³⁴ www.iss.it/cnmr

²³⁵ http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf

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). Since 2001, 215 Regional Centres have been designated by official regional decisions. 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.

According to the n. 279/2001 decree, each patient suspected to have 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 National Health System (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 (*Federazione Italiana Malattie Rare - FIMR*)²³⁶ 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.

Pilot European Reference Networks

Italy participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA, EPNET, EPI, EUROHISTIONET, NEUROPED, PAAIR, EN-RBD (main partner) and TAG.

Registries

The Italian National Registry for Rare Diseases, was established at ISS in 2001 in accordance with article 3 of Ministerial Decree 279/2001. It is located at Italian NCRD – ISS and it is supported by public funds. The general objectives include epidemiological surveillance of rare diseases, and planning and evaluating health care national programs. Specific objectives are: i) estimation of incidence and prevalence; ii) temporal and geographical distribution of cases and diseases at national level; iii) diagnostic delay. This registry is also a tool to support clinical research and to promote discussion among health professionals regarding the definition of diagnostic criteria. The National Registry collects the data coming from Regional registries. From 2002 onwards each Italian Region established its Regional Registry for rare diseases. These registries collect epidemiological information provided by accredited Centres for rare diseases (*Presidi* and *Centri*) 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. In fact, some of them have mainly epidemiological and public health purposes in support of 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. All steps concerning diagnosis, clinical follow-up and treatment are linked by a unique information system shared by all professionals involved in patients' management.

On November 2011 the Italian NCRD-ISS published the ISTISAN Report “National Registry and Regional / Interregional Registries for rare diseases”²³⁷, describing the surveillance system for rare diseases in Italy. Besides a background on the European initiatives on rare diseases, this Report provides detailed information of the evolution of Italian regulatory and institutional context; the steps towards planning and implanting the National Registry; the description of regional/interregional registries; the data quality assessment; the methodological models for estimating epidemiological indicators. Finally, the report describes the epidemiological results collected in years 2007-2010. The report highlights the strengths of this system for public health initiatives and its potentialities to stimulate research on specific rare diseases or groups of them. Up to 31 March 2011, 132,430 diagnostic schedules had been recorded, corresponding to 123,099 primary cases and 9,330 duplicate cases (7%). About 500 rare diseases were under surveillance in the National Registry. The more frequent notified group of diseases included hereditary coagulation disorders (7.5%; n = 9,825 cases), while the most frequent diseases were keratoconus (3.9% n = 5,148 cases) and amyotrophic lateral sclerosis

²³⁶ <http://www.uniampo.org/>

²³⁷ <http://www.iss.it/binary/publ/cont/undici20WEB.pdf>

(3.5%; n = 4,628). The National Registry is an important tool for epidemiological surveillance of rare diseases and for evaluating health care programs. The Registry has a strong legal support and it is in compliance with the legal and ethical requirements; it is a population-based registry but with different geographical coverage; it provides important public health indicators (patient mobility, delay in diagnosis), and it is a web-based registry. The National registry is linked to other interregional, regional and international registries.

Italy also participates in European registries such as EUROCAT, EIMD, EURO-WABB, 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 (the Italian Society of Metabolic Medicine and Newborn Screening), about one fifth of the Italian newborn population underwent an expanded screening in 2009.

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 Italian NCRD – 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 the EU. All relevant documents elaborated in the Tender and the final reports are available at the website www.iss.it/cnmr. In line with the results obtained during this Tender, in 2011 the Italian Ministry of Health funded a specific project on neonatal screening aimed at harmonising access to health services in the Italian Regions. The project, coordinated by the NCRD – ISS, is carried out in collaboration with the Ministry of Health, Italian Agency for Regional Health Services (AGE.NA.S), *Tavolo Interregionale Malattie Rare*, and two Italian Scientific Societies (SISMMESN and SIGU).

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. This census promoted by the *Società Italiana di Genetica Umana* (SIGU; Italian Society of Human Genetics) 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 immunogenetic analyses, and clinical activity, including genetic counselling. Certified quality systems adopted by the Institutes and the adequacy of some genetic tests have been also checked. The next survey concerning the 2011 data will be carried out in 2012.

In 2010, in collaboration with SIGU, a group of experts determined that changes were needed to improve the organisation of genetic services²³⁸. The study revealed that only 28% of the 278 Centres surveyed were certified according to quality standards. Moreover, the foetal karyotype was examined on either trophoblast or amniocytes in about one every 4.4 pregnancies and only 11.5% of cytogenetic analyses and 13.5% of molecular tests were accompanied by genetic counselling. This study gathered data from laboratories and services over a one-year period, including 217 molecular genetics and 171 cytogenetic laboratories, and 102 clinical genetic services. The authors of the study published in *Genetic Testing and Molecular Biomarkers* recommend reorganising the structure of genetic testing in Italy, which they qualify as oversized, and to improve quality management, as well as to access to pre- and post-test counselling. This study also underlines the necessity of transborder testing services because of a lack of availability to testing for many rare diseases in Italy.

Diagnostic tests are registered as available in Italy for 793 genes and an estimated 794 diseases in the Orphanet database²³⁹. Within the national framework there are consolidated procedures to send biological and genetic samples abroad when necessary.

²³⁸ <http://www.liebertonline.com/doi/abs/10.1089/gtmb.2009.0097>

²³⁹ Information extracted from the Orphanet database (September 2011).

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 use genetic tests. This activity is dependent on a Steering Committee, composed of experts who evaluate the results of cytogenetic and molecular genetic tests. All the 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 National Decree for all participant laboratories (public and private). At the end of each trial of external quality control each laboratory receives its own results. In addition, the NCRD – ISS organises a national Conference to illustrate the main results.

The NCRD-ISS is a member of the management board of the European Molecular Genetics Quality Network (EMQN²⁴⁰) 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.

National alliances of patient organizations and patient representation

In Italy, UNIAMO is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing over 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.

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 the following 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, which covers the whole Italian territory, started in 2009, and will conclude in 2012.
- "Galeno Help" results from a memorandum of understanding between UNIAMO and the Professional Pharmacists Union (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 suspected case to diagnosis of a 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.
- "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.

²⁴⁰ <http://www.emqn.org/emqn/Home>

- “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 included the Ministry of Health, 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.
- “The Diaspro Rosso” is aimed at identifying the social cost of rare diseases incurred by families.

The ISS hosted the activities of the National Council for Rare Diseases (the “*Consulta*”), established in September 2006 by a Directorial Decree of the Ministry of Health and Welfare: the Council was a national independent representative body, collaborating with the NCRD. 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 *Consulta*²⁴¹ 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 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.

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 currently 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 website²⁴².

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, which hosts the Italian Orphanet headquarters; Orphanet country coordinator and Scientific Director at Paediatric Hospital Bambino Gesù; President of Farindustria, which financed this second book; and President of Uniamo FIMR – the Italian Federation for Rare Diseases.

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.

²⁴¹ www.cndmr.it

²⁴² <http://www.orphanet-italia.it/national/IT-IT/index/homepage/>

At the end of 2011 OrphaNews Italia was launched with a first issue in December 2011: OrphaNews Italia²⁴³ 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.

Official information centre for rare diseases

The NCRD-ISS performs scientific research and public health activities, both at national and international level and since many years plays a key role in disseminating information on rare diseases through the official website²⁴⁴ 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 to 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 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 the NCRD-ISS on February 2008 and is funded by 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 NCRD-ISS web page²⁴⁵. 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 data, also using national and international databases (e.g. Orphanet, PubMed, ClinicalTrials.gov, etc.).

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 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.malattirari.it set up by UNIAMO, besides providing general information on legislative and administrative issues and orphan medicinal products, provides information at regional level thanks to the contributions of patient organisations and health professionals.

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 Consensus Conferences carried out by the NGS. Guidelines published by NCRD, as part of the NGS, include those for Down’s syndrome, alternating hemiplegia, hereditary epidermolysis bullosa.

With the aim to promote the development of high quality best practice guidelines and their use in Italy and across Europe, NCRD organises national and international training courses providing participants (health care professionals, policy makers, patients) with the opportunity to learn about the core methodology used to develop best practice guidelines. On November 2011, the NCRD organized the Course “Guidelines on rare

²⁴³ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=ItaliaNews>

²⁴⁴ www.iss.it/cnmr

²⁴⁵ www.iss.it/cnmr

diseases: basic principles for the development”. In addition NCRD encourages the international debate on role and quality of best practice guidelines in the field of rare diseases.

About 72 *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 Region²⁴⁶.

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 diseases²⁴⁷.

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 NCRD organises residential courses and learning activities dedicated to the empowerment of patients, health professionals and policy makers²⁴⁸. This program is included within the project “Rare diseases: from monitoring to training” funded by the Ministry of Health.

The NCRD and the ISS External Relations Office have developed in several Regions a project for training general practitioners (GP) and paediatricians to look for rare diseases, in order to reduce delay to 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. The next step for improving the training model will be to share it with patient organisations and to work with them.

The NCRD-ISS published the manual “Common stories of rare diseases: How to navigate the world of strange names”, in collaboration with the Psychoanalytic Institute for Social Research and Italian National Council of Social Work. This tool is addressed to train in rare diseases social workers and health and social professionals.

A relevant role in education of medical doctors is carried out by patient organisations (for example, UNIAMO’s projects “Knowing to assist” and “Mercury”, see the “National alliances of patient organisations and patient representation” section).

National rare disease events in 2011

Since February 2008, UNIAMO 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 dozens of local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV.

UNIAMO FIMR, in collaboration with its member associations, promoted and coordinated various events to celebrate the Rare Disease Day throughout Italy under the patronage of the President of the Republic of Italy. Events in 2011 to mark the day included the national event “*Rari ma uguali*” (Rare but equal). Orphanet Italy organised a communication campaign on rare diseases with the distribution of information material (a CD-Rom version of the book “*Annuario Orphanet delle Malattie Rare 2011*”, Orphanet Italy leaflets, Rare Disease Day pins, balloons, bandanas, etc.) at the Bambino Gesù Children Hospital in Rome. On 26 February 2011, in collaboration with the Barbareschi Foundation, UNIAMO organised an event at the Argentina Theatre in Rome to raise awareness on rare diseases.

On 20-26 February 2011 Mediaset and National TV channels aired a spot entitled “Mum, what are rare diseases?” promoted by UNIAMO FIMR. The alliance also announced the partnership of the Volley League A1

²⁴⁶ <http://malattierare.marionegri.it/content/view/111>

²⁴⁷ http://www.governo.it/bioetica/pdf/Malattie_rare_25112011

²⁴⁸ <http://www.iss.it/cnmr/appu/index.php?lang=1&tipo=56&anno=2011>

A2 with Rare Disease Day. During the weekend of 26-27 February 2011 all players of the 40 male and female teams wore rare disease T-shirts during their presentation while the speakers read a short message of information on rare diseases.

On 25 February 2011, the NCRD – ISS organised in Rome the final EUROPLAN conference and the first meeting of EPIRARE (European Platform for Rare Disease Registries). EUROPLAN and EPIRARE are coordinated by NCRD-ISS and are three-year projects co-founded by the European Commission within the EU Program of Community Action in the field of Public Health.

On 28 February 2011, the NCRD-ISS organised the ceremony "*Il Volo di Pegaso*" and the theatre show "*Controvento*", based on rare disease stories.

On 12 April 2011, the Besta Neurological Institute organised in Milan a workshop to show the results of a pilot study on social costs and welfare needs for rare diseases: the study was carried out by the Institute in collaboration with ISFOL (Institute for the Development of Workers' Professional Education), UNIAMO, Orphanet Italy, and Farmindustria.

On 4 June 2011, the Bambino Gesù Children Hospital organised in Gaeta a workshop on "Mass Media and Rare Diseases", to stress the role of media in disseminating knowledge on rare diseases, and the responsibility of the reporters in spreading sound information.

The NCRD-ISS organised in 2011 the following events: the 3th meeting on "Narrative medicine and rare diseases (Rome, 13 June 2011); "The communication challenge on rare diseases: words and images on display" (Rome, 14 June 2011); "Primary prevention of congenital anomalies" within the SANIT - International Health Forum (Rome, 14-17 June 2011); "Guidelines on rare diseases: basic principles for the development" (Rome, 21 November 2011).

On 1 July 2011, UNIAMO presented in Rome the project "A Community for rare diseases", aimed at developing a model to assess the quality of expert centres for rare diseases in Italy.

In December Telethon-Italy organised a fundraising event to promote research on genetic diseases.

Other events addressed to rare diseases included: 67th National Conference of the Italian Society of Paediatrics (Milan, 9 June 2011), Rotary Workshop on Rare Diseases – State of the Art and Operative Proposals (Rome, 17 June 2011), National Conference on Williams Syndrome (Rome, 24 September 2011), 16th Meeting of the Italian Society of Human Genetics (Milan, 14-15 November 2011), 11th National Meeting of Genetics, Immunology and Translational Paediatrics (Messina, 26 November 2011).

Hosted rare disease events in 2011

Amongst the hosted rare disease events in Italy this year and announced in OrphaNews Europe were: the Europlan Final Conference (Rome, 25 February 2011), 4th International Symposium on Pulmonary Rare diseases and Orphan Drugs (25-26 February 2011, Milan), Fifth Meeting on the Molecular Mechanisms of Neurodegeneration (13-15 May 2011, Milan), 8th International Health Forum, SANIT (Rome, 14-17 June 2011), EPIRARE kick-off meeting (Rome, 11 July 2011).

In addition to this, an international Medical Genetic Course was held under the sponsorship of Orphanet Italy at the Bambino Gesù Children Hospital in Rome on 23-24 June 2011. This event was addressed to doctors, biologists, researchers, medical students, with the aim of analyzing thoroughly clinical, biological and therapeutic aspects of some inherited rare diseases. A course was also organised by the European School of Oncology in collaboration with the Rare Care project in Stresa from 31 March – 1 April 2011, focusing on all the main rare solid cancers of the adult. The 3rd Goldrain Course in Prenatal Genetic Diagnosis took place from 15 to 21 October 2011 at the Goldrain Castle in South Tyrol. The 2nd Course in Eye Genetics-EuroMediterranean University Center of Bologna Eye Genetics was held in Bologna on 28 September – 1 October 2011: this 4-day long postgraduate level course is addressed to both researchers and clinicians seeking an up-to-date introduction to the field of ophthalmogenetics today.

Research activities and E-Rare partnership

National research activities

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)²⁴⁹, 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 diseases²⁵⁰ had a total budget of €8 million. The call for projects was published in 2008 and 13 projects were granted in 2010.

²⁴⁹ <http://www.agenziafarmaco.gov.it/>

²⁵⁰ http://www.quotidianosanita.it/cronache/articolo.php?&&articolo_id=1144&&cat_1=1&&cat_2=0

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 2011 Telethon was able to fund 230 research projects on genetic diseases thanks to fundraising activities in 2010.

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, CARDIOGENET, CUREHLH, CUREFXS, CLINIGENE, CONTICANET, CSI-LTB, ENRAH, EURADRENAL, EUCILIA, EUCLYD, EMSA-SG, EUROBONET, EUROGROW, EURO-LAMINOPATHIES, EUROPAPNET, EUROBNFS, 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, IPF-AE, HAE III, HMA-IRON, HSCR, KINDLERNET, 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, OSTEOPETR, PEROXISOMES, PNSEURONET, PROTHETS, PODONET, PEMPHIGUS, RD PLATFORM, RISCA, READ-UP, SIOPEN-R-NET, SKIN-DEV, SPASTICMODELS, SME MALARIA, STEM-HD, TAMAHUD, TUB-GENCODEV, TARGETHERPES, VITAL, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPATH.

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.

IRDiRC

The ISS and Italian Telethon Foundation are committed members of IRDiRC.

Orphan medicinal products^{251,252}

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 NCRD, 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.

²⁵¹ 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.

²⁵² 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.

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, 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 66 orphan medicinal products approved by EMA are launched on the market. The cost of 44 of them is fully paid by the National Health System (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 reimbursement²⁵³. 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 available²⁵⁴.

Orphan medicinal product pricing policy

Prices of all medicines for reimbursement by the National Health Service, 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.

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. 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. Many Regions in the last years have supplied class C drugs to their population. According to AIFA, the orphan medicinal product availability in 2010 included 6,839,423 daily doses (DDs), with a total cost of €661,709,750, while the corresponding total cost of non-orphan medicinal products was €12,981,636,953 for 21,971,349,308 DDs. Thus, the DDs cost for orphan medicinal products was about €100, compared to €1.60 for non-orphan medicinal products.

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 patient²⁵⁵.

Other initiatives to improve access to orphan medicinal products

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96²⁵⁶ (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 authorised²⁵⁷. A Ministerial Decree of

²⁵³ According to the Final Report of the European 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.

²⁵⁴ http://www.iss.it/binary/orfa/cont/Farmaci_orfani_in_Italia_Feb_2009.pdf (document accessed May 2011 and last updated in February 2009).

²⁵⁵ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Acces Issues*, Donald Macarthur (2011) p.83

²⁵⁶ 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).

²⁵⁷ KCE reports 112B: *Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* p.50.

8 May 2003²⁵⁸ 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 the NHS can also be decided by a doctor, as envisaged by article 3, paragraph 2 of Law Decree²⁵⁹ 23/1998, provided that this decision is made on a named patient basis, documented evidence is provided, and no other treatment is possible. “Fondo AIFA 5%” also finances the use of medicines with non-approved indications.

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 use²⁶⁰.

At the end of 2010, a new deal between central Government and the Regions will mean that ‘potential/important therapeutic innovations’ will be automatically included on regional formularies, so they should be available simultaneously and quickly across Italy¹⁵.

Orphan devices

No specific information reported.

Specialised social services

Respite care services are unevenly distributed within Italy and are mainly provided by governmental or accredited institutions and sometimes by the private sector: full or partial reimbursement is offered and some patient organisations provide services free of charge. A new act has been proposed defining the services that the entire population is entitled to; this includes “respite intervention” for families affected by severe disabilities, either in residential structures or semi-residential ones. 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 (for example, 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 year 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.

²⁵⁸ Ministerial Decree 8 May 2003 *Uso terapeutico di medicinale sottoposto a sperimentazione clinica* (published in GU 28 July 2003, n. 173).

²⁵⁹ 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).

²⁶⁰ *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

1.15. LATVIA

Definition of a rare disease

In Latvia, there is no official definition for rare diseases, as stakeholders in Latvia 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

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 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 centres of expertise for rare diseases in Latvia, but, for example, the Latvian State University Children's Hospital provides genetics services. 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).

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.

Pilot European Reference Networks

Latvian teams participate/participated in the following European Reference Networks for rare diseases: Dyscerne and PAAIR.

Registries

The National Health Service of Latvia is the supervising authority and keeper of State Register of patients with specific diseases. There is no separate register for rare diseases, but the register of the patients with specific diseases includes patients with cancer and congenital anomalies (some of these are rare diseases). Latvia contributes to the EURO CARE (Eurocare-5 study) European registry.

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 4 genes and an estimated 4 diseases in the Orphanet database²⁶¹.

²⁶¹ Information extracted from the Orphanet database (September 2011).

National alliances of patient organisations and patient representation

In 2009 the Latvian Rare Disease Organisation Caladrius²⁶² 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. In 2011 Caladrius (in collaboration with Latvian State University Children's Hospital) organised two visits of the high-qualified cardio surgeons: as a result, high-complicated operations were carried out for 11 children with inborn heart pathology. In 2011 Caladrius organised 4 seminars about methods of alternative therapy.

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. 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 abroad²⁶³.

Sources of information on rare diseases and national help lines

Orphanet activities in Latvia

Since 2006, there is a dedicated Orphanet team in Latvia, currently hosted by the Medical Genetics Clinic of the Latvian State at the Children's University Hospital, Riga. 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 Latvia for entry into the Orphanet database. The Ministry of Health of the Republic of Latvia has designated the National Health Service as the representative of the Republic of Latvia to participate in the Joint Action Orphanet Europe since April 2011. The Orphanet Latvia country site is in progress and the site will go on line in April 2012.

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

No information reported yet.

Good practice guidelines

No best practice guidelines for rare diseases have been produced at national level in 2011.

Training and education initiatives

No events reported yet.

National rare disease events in 2011

To mark Rare Disease Day 2011, the Latvian Rare Disease Organisation, Caladrius, organised informative seminar for public and media representatives about Genetic and rare diseases.

The Latvian Hemophilia Society organised meeting for people with rare bleeding disorders on 16-17 April 2011 to celebrate World Haemophilia day: this was most attended meeting in many years, people wore red as recommended by the global dresscode. Many professionals participated and event was mentioned in media.

²⁶² www.caladrius.lv

Hosted rare disease events in 2011

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.

E-Rare

Latvia is not currently a partner of the E-Rare project.

IRDiRC

Latvian funding agencies are not currently committed members of 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."²⁶⁴

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 register²⁶⁵ 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 2011: Arzerra, Cystadane, Diacomit, Gliolan, Glivec, INCRELEX, Kuvan, Litak, Mozobil, Nexavar, Nplate, Pedeia, Revatio, Revolade, Sprycel, Tasigna, Ventavis, Volibris, Wilzin, Myrin. In 2011, compared to 2010, 6 new orphan medicinal products were launched on the market: Kuvan, Litak, Mozobil, Nplate, Revolade, Tasigna and 4 orphan medicinal products are no longer available on the market: Atriance, Evoltra, Exjade, Orfadin.

²⁶⁴ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp16-17)

²⁶⁵ <http://www.zva.gov.lv/index.php?id=112&top=112&large=>

Orphan medicinal product pricing policy

No specific policy is in place.

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.

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: Exjade, Revatio, Volibris, Nexavar, Atriance, Cystadane, Wilzin, Diacomit.

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)."*²⁶⁶

Orphan devices

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

A working group was established by Order No. V-564 of 1 Jun 2011 of the Ministry of Health of the Republic of Lithuania to frame the National Plan on activities related to rare diseases which will be finalised for the second half of 2012. Representatives from the universities, university hospitals, non-governmental organisations of patients and medical professionals as well as state institutions (Ministry of Health, the National Health Insurance Fund, the State Medicines Control Agency) are involved in the working group.

Expenses for health care services and drugs are reimbursed from the Compulsory Health Insurance Fund budget as for other groups of patients. 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).

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

²⁶⁶ *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. An outpatient clinic for cystic fibrosis patients was established in 2011.

Pilot European Reference Networks

Lithuanian teams participate, or have participated, in the following European Reference Networks for rare diseases: ECORN CF and PAAIR.

Registries

Lithuania contributes to the EUROCARE CF registry. 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.

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.

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 4 genes and an estimated 3 diseases in the Orphanet database²⁶⁷. In December 2011 Lithuania delivered an extended list of genes and diseases (available for diagnostics) and now is waiting for approval.

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.

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. 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 Lithuania²⁶⁸ national website in Lithuanian.

Official information centre on rare diseases

The only official common information source on rare diseases in Lithuania - is Orphanet.

²⁶⁷ Information extracted from the Orphanet database (September 2011).

²⁶⁸ <http://www.orpha.net/national/LT-LT/index/prad%C5%BEia/>

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

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”²⁶⁹ 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 2011

Various rare disease patient organisations invited the public to participate in various events, and also organised online publications and articles in the newspapers to mark Rare Disease Day.

The Centre for Medical Genetics in Vilnius University Hospital Santariškių clinics issued an online invitation via their internet portal to commemorate the Rare Disease Day 2011. The Orphanet-Lithuania coordinator attended the Morning News talk show on national TV, where he spoke about the problems that patients and their families face when dealing with rare diseases in Lithuania in particular.

The Lithuanian Association for the Genetic Neuromuscular Disorders “Sraunija” produced a play entitled “Little Prince” where the main character was a boy with a rare disease. An interview of the Lithuanian Cystic Fibrosis Association chairman and a pediatric neurologist was released in the press on that day. A representative of the Rare Disease Initiative spoke on national radio to raise awareness of the lack of information about rare diseases and the problems of families affected by these disorders. A clinical geneticist was also interviewed on national radio about rare diseases in Lithuania and other countries, and the diagnostic and treatment possibilities.

A section on rare diseases took place in the 2011 Paediatric Congress in Vilnius.

Hosted rare disease events in 2011

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.

²⁶⁹ <http://www.pediatrija.org>

Participation in European research projects

Lithuanian teams participate, or have participated, in the EUROPEAN LEUKEMIA NET research project.

E-Rare

Lithuania is not currently part of the E-Rare consortium.

IRDiRC

Lithuanian funding agencies are not currently committed members of 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 Agency²⁷⁰ 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), Pedea (ibuprofen), Revatio (sildenafil), Rvlimid (lenalidomide), Revolade (eltrombopag), Sprecel (dasatinib), Tasigna (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 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*²⁷¹ 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)."

²⁷⁰ <http://www.vvkt.lt/>

²⁷¹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (p17)

Other initiatives to improve access to orphan medicinal products

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.

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 will work out a national plan for rare diseases based on the results of a survey 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 2011²⁷².

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.

²⁷² *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>

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.

Centres of expertise

There are currently no official centres of expertise for rare diseases in Luxembourg.

Pilot European Reference Networks

Luxembourg does not currently participate, or has not participated, in any European Reference Networks for rare diseases.

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 rare diseases: the association organises informative events, counselling, guidance and self-help groups and is involved in the work of the Task Force on Rare Diseases Luxembourg.

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 2011

To mark Rare Disease Day 2011, the Ministry of Health of Luxembourg together with the National Interdisciplinary Rare Disease Working Group has organised a press conference on 28 February 2011 to launch the national report : "Rare diseases: a national survey on the situation of persons with rare diseases in

Luxembourg.²⁷³ In 2005, following the European Conference on Rare Diseases held under Luxembourg's Presidency of the EU, an interdisciplinary working group was constituted, gathering medical experts, neurologists, paediatricians, biological specialists, experts in metabolic diseases, the patient's association ALAN and the Ministry of health. The objective was the constitution of a platform for the interdisciplinary exchange, the study of the situation in Luxembourg and the elaboration of initiatives for improvement

The analysis of the situation of rare diseases in Luxembourg was a priority. The objectives of the study were to evaluate the burden of disease of rare diseases in Luxembourg, to analyse the medical and psychosocial care the patients receive, to collect feedback on problems and needs (in the medical, social, education, professional and leisure area), to evaluate the strengths and weaknesses of the health and social security system as concerns rare disease patients. Based on the results of the inquiry recommendations were formulated for the elaboration of a National Plan for Rare Diseases.

Hosted rare disease events in 2011

No hosted events were reported in 2011.

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 are not currently partners of 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

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.

²⁷³ *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>

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 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. A detailed framework that will form the basis for a national strategy for rare diseases is being created. The plan is to propose a request for a first budget for the strategy of rare diseases from the National Budget for 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 through a bilateral health agreement between the two countries. Further bilateral agreements with other EU Member States are being sought, developed and completed.

Pilot European Reference Networks

Teams from Malta do not currently participate in European Reference Networks for rare diseases. Due to the small size of Malta and its population, participation in the future European Reference Networks will probably be only feasible on the level of individual experts or group of experts managing different cases of rare diseases or groups of rare diseases. Furthermore, there is only one potential centre of expertise 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 2013 onwards it is also planned to house the new Oncology Hospital which is currently under construction on the Mater Dei Hospital site.

Registries

Malta contributes to the EUROCAT European registry as well as the RARECARE and EUROCCARE projects through the Malta National Cancer Registry.

Neonatal screening policy

Neonatal screening is available for haemoglobinopathies and hypothyroidism.

Genetic testing

Genetic studies (karyotyping and molecular genetic studies) in fetuses 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 centre abroad, mainly to NHS labs in the UK. 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. However, this role is increasingly being assumed by the Malta Health Network²⁷⁴ which is a network of health-related voluntary organisations in Malta ().

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 2011.

Good practice guidelines

No best practice guidelines for rare diseases have been produced at national level in 2011.

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 2011

Malta did not commemorate RDD in 2011. However, RDD in 2012 was commemorated by the Malta Health Network (MHN) in collaboration with the Ministry for Health, the Elderly and Community Care (MHEC). Funds are being earmarked for Malta's participation in the upcoming Rare Diseases Day in future years.

Hosted rare disease events in 2011

No rare disease events were hosted in Malta in 2011.

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, Ithantet and the University of Malta). According to the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, *"measures [...] are being taken to promote research and development in Malta. Enterprises carrying out research and development are entitled to various tax credits according to the nature of the specific investments. These tax credits are in addition to the standard 100 % deductions allowed under the Income Tax Act (Cap. 123). These credits are granted under a general framework, which applies to all Research and development initiatives and not exclusively to the pharmaceutical sector²⁷⁵".*

Participation in European research projects

Teams from Malta do not currently participate in a European research projects for rare diseases.

E-Rare

Malta is not currently a partner for the E-Rare project.

IRDIRC

Maltese funding agencies are not currently committed members of the IRDiRC.

²⁷⁴ <http://www.maltahealthnetwork.org/>

²⁷⁵ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp17-18)*

Orphan medicinal products

Since the start of 2010 Malta has 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

Information gathered by the Medicines Authority 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, 38 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 Exceptional Medicines Treatment Policy allows for specific provisions for the reimbursement of orphan medicinal products. In 2011, three orphan medicinal products have been introduced into the Government Formulary List and access to treatment has also been granted according to the Exceptional Medicines Treatment Policy.

The following orphan medicinal products are currently being reimbursed²⁷⁶: Amifampridine, Anagrelide, Azacitidine, Bosentan, Caffeine citrate, Celecoxib, Cinacalcet, Cladribine, Clofarabine, Colistimethate sodium, 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, Rufinamide, Sildenafil, Stiripentol, Sulfadiazine, Sunitinib, Thalidomide, Thiotepa, Tiopronine, Tobramycin (inhalation solution), Topotecan, Vigabatrin. The drugs available within the National Health Scheme are on the national Government Formulary List and available for dispensing, free of expense to the patients entitled to them.

Other initiatives to improve access to orphan medicinal products

Approval for Compassionate use is a regulatory procedure. It refers to the use of the product which is being considered for approval under the centralised procedure in line with Regulation 726/2004. 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.

Orphan devices

There are no specific initiatives in place concerning orphan devices in Malta. Indeed, during the open consultation on the Commission Communication “Rare diseases: Europe’s challenges”, Malta expressed the view that an EU regulation on orphan medical devices “*would neither be necessary nor beneficial*” and that the “*current legal framework already caters for rare diseases*”²⁷⁷.

²⁷⁶ Source: Directorate of Pharmaceutical Affairs, Ministry of Health the Elderly and Community Care (13 March 2012)

²⁷⁷ http://ec.europa.eu/health/archive/ph_threats/non_com/docs/r082_en.pdf

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 a private foundation (Inspire Foundation, formerly the Eden Foundation). 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, for the time being, 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 Netherlands regarding rare diseases for the years 2012-2015²⁷⁸. Some important points in this report are the following:

- Strengthening the role of university hospitals with regard to patient care and research in rare diseases;
- Funding 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 some time in 2013, neither of the changes will jeopardise the accessibility of orphan medicinal products);
- A separate scientific programme is indicated (already started in 2011);
- 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 additional 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 the national strategy initiated by the government for 2012-2015, preparations for a national plan on rare diseases for all stakeholders have started. The input of all stakeholders was collected via information from different meetings organised by several stakeholders in the last years and via newly installed working groups in 2011 and a new website and is coordinated by the Dutch Steering Committee on Orphan Drugs. This process will be continued in 2012 under the auspices of a sounding board especially formed for this task. On 1 October 2011 the site <http://www.npzz.nl/> was launched in order to collect input for the national plan for rare diseases in a systematic way. The National Plan for Rare Diseases with input from all stakeholders is in an advanced stage of preparation, anticipated to be ready before summer 2012^{279,280}. The national plan will

²⁷⁸ An English language translation of the annex is under preparation.

²⁷⁹ Following the adoption of the European Union Council Recommendation in June 2009, the Dutch government took no immediate initiatives to support a national plan/strategy for rare diseases. The reason being that there was already a 'strategy' in place since 2001 aimed at patients with rare disorders and at providing information about and accessibility of orphan drugs, embedded in wider

consist of four chapters comprising the issues of information, care, research and availability of knowledge (education) and availability of therapy. However, within the purview of the Recommendation of the Council, the national plan will be incorporated into the national strategy. Stakeholders are, on the other hand, free to develop and implement initiatives on their own.

Centres of expertise

All stakeholders – and also the government - support the idea that the (follow-up) care 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 Rare Disease Task Force's working group on Standards of Care. The Dutch Federation of University Medical Centres started to make an inventory of existing expertise at national level in 2010 and the discussion on the definition of 'centres of expertise' has been initiated. Currently, the eight university medical centres in the Netherlands function as the main clinical reference centres for specific rare diseases. Other highly specialised care hospitals may also function as well-coordinated centres. However, only university hospitals are entitled to the reimbursement of clinically applied orphan medicinal products. The number of clinical reference centres for rare diseases varies considerably in the Netherlands, e.g. there are 13 government-appointed haemophilia centres, 6 centres for cystic fibrosis, 2 for MPS, and one each for Gaucher disease and Fabry disease. University medical centres provide genetic testing and counselling and run clinics in regional hospitals.²⁸¹

Pilot European Reference Networks

The Netherlands participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUROHISTIONET, NEUROPED, Care-NMD and PAAIR (main partner).

Registries

There is no comprehensive national patient registry in the Netherlands, but several patient registries exist for specific rare diseases, including registries maintained by patient organisations and at the main clinical reference centres. The Dutch Orphan Disease Registry Consortium, established at the end of 2008, consists of several partners including four academic research groups, two pharmaceutical industry companies, three patient organisations, The Health Care Insurance Board and the Steering Committee on Orphan Drugs. This consortium aims to build an innovative, comprehensive, sustainable orphan disease registry framework that provides a practical and transparent approach to collect information on rare diseases, to encourage orphan medicinal product development and to optimise patient care. The group of rare inborn errors of metabolism, including lysosomal storage disorders, is used as the first model group of diseases to build such a registry framework. In this context the national web-based facilitating registry for inborn errors of metabolism has been developed further: the Dutch Diagnosis Metabolic Diseases Registry. The societal value of the DDRMD became obvious in 2010 as questions on the incidence of metabolic disorders from several interested parties can be answered now.

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). Furthermore, The Netherlands contributes to European registries including EIMD, TREAT-NMD, AIR, EUROCARE CF, EPCOT and EUROCAT.

governmental policies. This 'strategy' had a ten year time line. Nevertheless, the Steering Committee on Orphan Drugs along with the Dutch Genetic Alliance VSOP and the Forum Biotechnology and Genetics (FBG), lobbied for a national plan to be put on the political agenda, and both stated their intention at the 2010 Europlan National Conference on Rare Diseases to cooperate with stakeholders to prepare a national plan. Moreover, the Steering Committee on Orphan Drugs expressed their concerns about the preparation of a Dutch plan to the Minister of Health in December 2010.

²⁸⁰ In a letter to the Minister of Health with a copy to Parliament, VSOP reacted rather critically on the ministers' strategy report, stating that she depicted the situation and governmental efforts too positively, leaving several real problems unaddressed, for example related to the lack of reference centres, the lack of a national registration, and the lack of standards of care.

²⁸¹ The Steering Committee on Orphan Drugs recommends the establishment of an independent body that will identify and periodically review the centres of expertise on the basis of the aforementioned criteria. This recommendation was forwarded to the Ministry of Health, Welfare and Sport. However, the Ministry will wait at least two years for results regarding the development of centres of expertise / reference centres for rare diseases in university hospitals.

Neonatal screening policy

On 1 January 2007, an extended neonatal screening program was launched in the Netherlands, for 18 rare disorders: phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis, 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 Netherlands (RIVM, VUMC and VSOP) was involved in the EC project “Evaluation of population newborn screening practices for rare disorders in Member States of the European Union” funded by the EC/EAHP, that started in 2010. This project aimed at identifying and evaluating all aspects deemed relevant to the implementation of a public health action in neonatal screening resulting in a report on the practices of neonatal screening for rare disorders implemented in all the Member States. This report was published in the beginning of 2012.

Thanks to developments in both therapy as well as screening methodologies, some of the lysosomal storage disorders may soon meet the criteria set by the Health Council of the Netherlands in 2005 for the national neonatal screening program. Most lysosomal diseases have a broad clinical spectrum and neonatal screening will probably not just identify patients who will develop symptoms within a few months after birth, but also persons who will develop symptoms at later age. The ethical, legal and societal aspects of neonatal screening for some lysosomal storage disorders are being investigated by two Dutch research groups.

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.

Genetic testing

Genetics services in the Netherlands are funded by the health insurance through a special budget; services include genetic counselling, chromosome analysis, biochemical (enzyme) diagnostics and DNA-diagnostics. All 8 University medical centres are licensed for clinical genetics; to provide counselling and pre- and postnatal testing. 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. 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 disorders usually performed in one laboratory only. Expertise and research is leading in the portfolio of tests offered. Together the 8 Dutch laboratories for DNA-diagnostics offer tests for over 900 genes²⁸².

Diagnostic tests are reimbursed by health care insurance 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. Testing upon request without an indication (for instance preconception cystic fibrosis testing) was not available until the end of 2010²⁸³.

National alliances of patient organisations and patient representation

The development of a national alliance of rare disease patient organisations is under discussion by stakeholders. VSOP²⁸⁴ represents about 65 member patient organisations for rare and genetic conditions, thereby acting as the national alliance for these patient organisations in the Netherlands. Specific attention is given to perinatal care, biomedical research, prevention, standards of care, ethical and societal issues. Some more common disorders are also represented in the VSOP membership. VSOP has a focus on the specific problems of rare disorders and represents EURORDIS in the Netherlands, but where there are several other patient umbrella organisations are dealing with (more general) health interests of relevance to people with rare disorders, such as the general organisation of health care (NPCF) and issues in the field of income and social participation (CG-Raad). VSOP participates in the Health Council, the RIVM (prenatal and neonatal screening), Forum Biotechnology and Genetics, ZonMw programs for health research, and several other health and health research policy platforms and committees.

²⁸² A list is available on the website www.DNA-diagnostiek.nl.

²⁸³ www.vumc.nl/cftest offers CF carrier testing for 150€

²⁸⁴ www.vsop.nl

In 2012, the government decided to decrease the budget for patient organisations from 43 to 25 million Euro's per year in the period 2012-2015, resulting in a minimum exploitation subsidy of € 25,000 and a maximum of €35,000 for a disease-specific organisation per year (previously, the maximum was €125,000). The exploitation subsidy for VSOP will end per 2014, therefore making VSOP fully dependent on project acquisition and donations.

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 VU University Medical Centre, Amsterdam and 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, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Netherlands²⁸⁵ national website in Dutch which was launched in 2011.

A collaboration has been established with Erfocentrum - the Dutch National Genetic Resource and Information Centre - and Orphanet. 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.

Official information centre for rare diseases

Until the end of 2011, the Steering Committee on Orphan Drugs functioned as an information centre for rare diseases and orphan medicinal products in the Netherlands. The secretariat of the Steering Committee answered various questions from pharmacists, medical specialists, patients and their families and pharmaceutical companies about rare diseases and orphan medicinal products. Furthermore, the Steering Committee had a signalling function in response to problems that are reported to the steering committee. Their website www.orphandrugs.nl provided general information.

As of 31 December 2011, the Steering Committee was disbanded by the government: however €880'000 was made available to ZonMw (the Netherlands Organisation for Health Research and Development) for the years 2012-2015 to install a secretariat for rare diseases and orphan medicinal products.

Help line

The most specialised and most used help line for rare disorders is the Erfocentrum ERFO line, providing information on genetic and rare diseases and pregnancy/reproduction related questions. Meldpunt (Information Desk from the Dutch Consumer and Patient Federation NPCF) is a more general health line for information concerning social services and health care insurance. However, for 'new' patients or parents, specific and reliable information may be still difficult to find, which will be addressed in the working out of the National Plan.

Other sources of information on rare diseases

The National Genetic Resource and Information Centre (Erfocentrum), founded by the VSOP, has both a board of representatives of patient organisations and medical professionals and hosts the national helpline for information on genetic issues and rare diseases. The website www.erfocentrum.nl contains a database of rare diseases with information for both lay-persons and professionals (www.erfelijkheid.nl). In addition, public information is available on genetic, biomedical and pregnancy related issues²⁸⁶. The Erfocentrum runs since 2010 a new website (www.erfelijkheidinbeeld.nl) which hosts all kinds of videos, DVDs, and presentations produced by patient organisations on phenotype and hereditary and/or congenital disorders. Using this new portal, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

²⁸⁵ <http://www.orpha.net/national/NL-NL/index/homepage/?lng=FR>

²⁸⁶ These sites provide further web based information: www.biomedisch.nl; www.zwangernu.nl; www.zwangerwijzer.nl; www.slikeerstfoliumzuur.nl; www.prenatalescreening.nl

The VSOP also functions as a centre providing expertise and advocacy for patient organisations for rare and genetic disease. 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.

Information on neonatal screening is available from the National Institute for Public Health and the Environment²⁸⁷, 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.

Good practice guidelines

In 2011, VSOP finished 30 out of 33 treatment guidelines for general practitioners as part of the project 'The patient as an information carrier', carried out in close collaboration with the patient organisations and the Dutch College of General Practitioners (NHG). Funding was provided by a Dutch health insurance fund (Innovatiefonds) for the production of guidelines. VSOP also continued to work on 17 standards of care for rare disorders, 4 of which will be finished in 2012, the others will be finished by 2014. Major funding (in total nearly €3million) was provided by the Dutch government.

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 a growing interest has been observed in university students to follow a lecture or 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 website²⁸⁸.

In addition, a course on practical clinical, radiological and pathological diagnosis of skeletal tumours was organised by the European network of excellence EuroBoNeT in collaboration with Leiden University Medical Center (14-16 February 2011).

National rare disease events in 2011

The Dutch Rare Disease Day 2011 was held on 15 May 2011²⁸⁹ in Artis ZOO, Amsterdam, in conjunction with the EURORDIS Conference. About 350 people, especially families, attended this meeting and two so called angel awards were granted for excellence in patient advocacy and medical care for rare diseases. This day was organised by the Dutch Steering Committee on Orphan Drugs, the Dutch Rare Disease Fund, the Pharmacists Association KNMP and VSOP. On 12 May 2011 a conference was organised by the Dutch member organisations of EURORDIS in collaboration with the Dutch Steering Committee on Orphan Drugs on care for rare diseases.

On 25 February 2011 the Patient Platform Rare Diseases organised a hearing event on rare diseases in the Dutch Senate in The Hague.

Hosted rare disease events in 2011

In 2011 the following rare disease related events were hosted by the Netherlands and reported in *OrphaNews Europe*: Optimal Role of Patient Organisations in Drug Development (24 March 2011, Amsterdam), 11th International Congress of the European Society of Magnetic Resonance in Neuropediatrics (24-26 March 2011, Amsterdam), The Third Birt-Hogg-Dubé Symposium (11-12 May 2011, Maastricht), Membership Meeting of EURORDIS, Amsterdam (13-14 May 2011), European Society of Human Genetics Conference, Amsterdam (28-31 May 2011).

²⁸⁷ www.rivm.nl/pns/hielprik

²⁸⁸ For instance information for screeners and information on the diseases screened: www.rivm.nl/pns/hielprik/films.

²⁸⁹ www.zeldzameziektendag.nl

Research activities and E-Rare partnership²⁹⁰

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. For the programme €13.6 million is available. The first call was launched in early 2011. ZonMw has also provided and continues to provide funding through several research programmes for research on rare diseases (e.g. the Innovative Research Incentives Scheme, the Gene Therapy subsidy scheme and the additional research programme on efficiency of Expensive and Orphan Medicines).

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 (Innovation Subsidy Collaboration projects (IS), Subsidy programme on exploiting knowledge and Technostarters) 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. However for practical and cost-effectiveness reasons the infrastructure currently can only accept rare disease samples when they are part of biobanks of 1000 samples or more, so the infrastructure for now mostly concerns, rare diseases samples when they are part of a biobank for a more common disorder²⁹¹.

Participation in European research projects

The Netherlands participates, or has participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BIGHEART, BIONMD, CARDIOGENET, CHEARTED, BIOMALPAR, BNE, CELL-PID, CONTICANET, CURE-FXS, CRUMBS IN SIGHT, ELA2-CN, DIALOK, EDAR, EMVDA, EMINA, EUCLYD, EuPAPNet, EURO-CGD, EUMITOCOMBAT, EUNEFRON, EUROBONET, EURAMY, EUROCARE-CF, EUROAGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, EVI-GENORET, EUROSD, EUROPADNET, EUROSTEC, HSCR, GENESKIN, GEN2PHEN, GENTECH, GENCODYS, GRIP, HDLOMICS, IMMUNOPRION, MLC-TEAM, NEMMYOP, NSEuroNet, NEUROSISS, NMD-CHIP, NOVSEC-TB, MITOCIRCLE, MITOTARGET, MMR-RELATED CANCER, MYASTAID, NEUROPRION, OLIGOCOLOR, PEROXISOMES, PERSIST, PNSEURONET, PRIBOMAL, PWS, TB-DRUG, TREAT-NMD, VACCINES4TB, VITAL, RD PLATFORM, and REVERTANT-EB.

E-Rare

The Dutch Organisation for Health Research and Development (ZonMw) and the Dutch Steering Committee Orphan Drugs participates in E-Rare 1 (2006-2010) and E-Rare 2 (2010-2014), and participated in the 2nd Joint Transnational Call in 2009 (€1.7 million was granted in funds for 14 Dutch research groups, involved in 9 of the 16 funded projects/consortia). The Netherlands did not participate in the 3rd E-Rare Joint Transnational Call (2011) but will participate in the 4th focused Joint Transnational Call (2012).

²⁹⁰ This section has been written using the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp53-62).

²⁹¹ Another interesting example is the following: 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. In the case of chronic conditions and fast-acting medicines for symptomatic treatment, it might be justified to collect evidence of efficacy from a trial treatment of a single patient. A "n of 1" is a clinical trial involving a single patient, i.e., a single case study. Through this service, patients with rare diseases would be able to receive treatment while at the same time testing the effectiveness of certain (expensive) medicines. During such an "n-of-1 trial" the physician alternately treats the patient with the off-label medicine and the medicine with which it is compared, for example, a placebo or treatment-as-usual. Rules are agreed in advance to allow for a fair comparison. The results of the trial treatment indicate whether the patient experiences benefits of the off-label medicine over and above treatment-as-usual. As series of trial treatments together bring more knowledge, these separate n-of-1 trials would be centrally coordinated and combined for analysis by an n-of-1 trial service. The current project is investigating 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. In a follow-up project, researchers hope to actually invite patients to participate in pilot trial treatments for neuromuscular diseases and eventually other diseases as well.

IRDIRC

The Netherlands Organisation for Health Research and Development (ZonMw) and the pharmaceutical enterprise Prosensa, are committed members of the IRDiRC.

Orphan medicinal products^{292,293}

Orphan medicinal product committee

The Steering Committee on Orphan Drugs (Stuurgroep WGM) was established in 2001 by the Minister of Health: its mission was to encourage the development of orphan medicinal products and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases. This committee was an independent organisation and the members are representatives of umbrella organisations for patients and for pharmaceutical companies, physicians, a pharmacist, a representative of the Dutch medicine evaluation board a representative of the Dutch health insurance board. The Steering Committee was involved in the EC projects E-Rare, Europlan and Polka. The action plan for this committee from 2008-2011 covered three priority areas: 1) improved access to health care and treatment through centres of expertise, 2) the stimulation of research and development of Orphan medicinal products, 3) the creation of a sustainable reimbursement system. The budget of this committee was €450,000 per year. 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 will no longer exist 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 (with extra funding) 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.

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.

Free advice was available from the Dutch Steering Committee on Orphan Drugs until the end of 2011. 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 pharmaco-economic 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. Analysis has shown that pharmaceutical SMEs are the engine behind orphan medicinal product development. The scheme will continue up to November 2016 with a total budget of €150,000. The scheme consists of two types of applicants – SME with ODD experience and SME without experience – and two types of subsidy – €7,200 and €3,600. Depending on their ODD experience, SMEs are allocated the large or small subsidy, provided their proposal meets all the formal criteria. A maximum of two ODD-support applications are permitted per SME per year. Five grants have been awarded at the end of 2011.

Orphan medicinal product market availability situation

In the Netherlands, all orphan medicinal products with EU market authorisation are available on the market.

²⁹² This section has been written using *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp53-62)

²⁹³ This section was 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)* (pp21-23)

Orphan medicinal product pricing policy

The pricing policy of orphan or non-orphan medicinal products is similar.

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, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Prialt, Replagal, Revatio, Revlimid, Revolade, Siklos, Soliris, Somavert, Sprycel, Tasigna, Torisel, Tracleer, Ventavis, Vidaza, Volibris, 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, Firazyf, Gliolan, Inovelon, Litak, Mepact, Mozobil, Pedea, Photobarr, Peyona, Plenadren, Riloncept Regeneron, Savene, Tepadina, Thalidomide, TobiPodhaler, Trisenox, Votubia, VPRIV and Vyndaquel.

For the use of orphan medicinal products in university hospitals, a reimbursement method ("*beleidsregel weesgeneesmiddelen*") was introduced from 1 January 2006, to increase the use of orphan medicinal products for treating rare diseases. The costs of the orphan medicinal products in university hospitals, in case they are accepted under this specific regulation, are totally refunded for a maximum of four years. In this period of temporarily refunding more information has to be collected on the efficiency of the product. After four years a re-evaluation takes place and the product may be listed permanently on the "*beleidsregel weesgeneesmiddelen*". For orphan medicinal products used outside the hospital (at home) there is a special reimbursement rule at the Medical Reimbursement System (GVS). Reimbursement can be asked for at the Health Care Insurance Board in case of off-label use in less than 1:150,000 inhabitants (i.e. less than 110 patients in the Netherlands). If a patient is chronically ill, they can request a personal budget (PGB) to obtain home care.

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.

Orphan devices

There are no initiatives regarding orphan devices.

Specialised social services

Respite care services are available, however not structurally imbedded in the general health care system. Organising respite services is left to private initiative, with or without funding from a health insurer. The personal budget (PGB) for patients who are dependent on non-medical care (due to disease, old age or handicap) can also be employed for respite care.²⁹⁴ These services include in-home respite, emergency respite, sitter-companion services, and therapeutic day care. A specialised nursing home for those with Huntington disease is run by the Health Insurance. Other therapeutic recreational services are provided by patient organisations, such as holiday homes for those with ataxia and neuromuscular diseases and camping car rental for Duchenne patients: patients may be asked to participate in the payment of such services. Social support, supported employment and support in travelling are available in order to help the integration of patients in daily life.

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

²⁹⁴ However, certain changes were made in the PGB as of 2012 that will make funding of respite care more difficult.

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

Although in 2011 a national plan or strategy for rare diseases was not yet adopted, significant steps have been undertaken towards the goal of adopting this important document in order for Poland to meet the EU Council Recommendation, hopefully by the end of 2012.

The existing National Health Program covers some issues of the rare diseases e.g. National Program Against Cancer, which is focused on improving early diagnosis and treatment of cancer, a majority of them being rare diseases. There is currently no specific budget dedicated for rare diseases within the framework of the entire health care system. This does not mean that the treatment of rare diseases is ignored by the Polish health care system. All diagnosed cases of rare diseases are treated in the framework of general health care, and in cases when reimbursement of orphan medicinal products is decided, several therapeutic programs with the use of these drugs are in place. The level of reimbursement of orphan medicinal products in the therapeutic programs on rare diseases in 2011 was around €50 million.

The Rare Disease Task Force was established via an order of the Minister of Health as his advisory body in 2008. The group consisted of: the Undersecretary of the State as its leader, representatives of some Departments of Ministry of Health, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Agency for Health Technology Assessment in Poland, National Health Fund, patient organisations, pharmaceutical industry and scientific experts. The main tasks of the Team were to present opinions on rare diseases policy and reimbursement of orphan medicinal products.

The setup of the Rare Disease Team changed in July 2011. The Minister of Health recognised rare diseases as a much broader problem, not only limited to orphan medicinal products, thus it was necessary to create a better tailored Task Force with competence also in healthcare system organisation and doctors' education. According to the new order of the Minister of Health the new Task Force leader was chosen based on his experience in the healthcare management rather than the official position. The sole purpose of the reorganised Task Force is to prepare a National Plan on Rare Diseases (NPRD). In autumn 2011 a new setup of this advisory body was formally constituted to help with the elaboration of a plan, in collaboration with patient organisations, due to be launched by the end of 2012. Due to the new Order of the Minister of Health, the group was reconstituted, and now it includes the following members chaired by a representative of the Ministry of Health: four experts in the field of rare diseases including representative of umbrella patient organisations, representatives of Poland in EU institutions in the field of rare diseases, Directors of the Departments at the Ministry of Health and representatives of National Health Fund (the Payor).

A National Conference on Rare Diseases²⁹⁵ organised by the Polish Cystic Fibrosis Foundation MATIO and the National Forum for the Therapy of Rare Diseases on 22 October 2010 in Krakow, using the recommendation of Europlan evaluation model, led in 2011 to the initiation of broad, multi-session work on the draft of national plan for rare diseases.

On 7-8 December 2011 the conference "Partnership for the National Plan for Rare Diseases", organised by National Forum for the Therapy of Rare Diseases was held in Warsaw. It was agreed during this conference that a patient's input to the draft concerning a National Plan on Rare Diseases should be prepared by the end of February 2012, based on data from the working-groups, and in accordance with the Europlan project. The draft will encompass different areas and aspects of rare diseases, such as classification and rare diseases registry; diagnostics; medical care; integrated social support; and information and education. Once prepared, the document will be presented to the Polish Ministry of Health for further discussion and elaboration.

Based on the above mentioned initiative, with the support of the Chairman of the ministerial Rare Diseases Task Force as well as the Children's Memorial Health Institute, the series of working meetings were organised in order to elaborate the final drafts of each mentioned area of the future national plan. During these several working sessions held in late 2011, it was decided that the working document "The systemic assumptions for the development of the National Plan for Rare Diseases" (a joint initiative of the National Forum for Therapy of Rare Diseases and broad rare diseases medical/scientific community) will be submitted directly to the Rare Diseases Task Force at the Polish Ministry of Health for further official elaboration of the

²⁹⁵ <http://www.europlan.org.pl/> and http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_poland_europlan.pdf

future governmental RD National Plan²⁹⁶. The entire initiative was launched following the EU Council Recommendation on the involvement of patients and their representatives in the political process and promoting the activities undertaken by rare diseases patient groups and associations.

Centres of expertise

In Poland, the health care of 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. There is a national coordinating centre for metabolic rare diseases at the Children's Memorial Health Institute in Warsaw with links to regional centres. Significant progress has been made as a result of the European Project of Centres of Excellence "PERFECT" QLG1-CT-2002-90358. The grant programme included problems associated with rare paediatric diseases in the field of genetics, metabolism, gastroenterology, cardiology, immunology and oncology.

Pilot European Reference Networks

Polish teams participated/participate in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, EPI/EPNET, EUROHISTIONET, PAAIR, European Network of Paediatric Hodgkin's Lymphoma and Care-NMD.

Registries

In Poland there are number of well constructed registries 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, ERCUSYN, TREAT-NMD, EURO CARE 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. This is coordinated by the Institute for Mother and Child in Warsaw. An additional 19 metabolic disorders diagnosed by tandem mass spectrometry (MS/MS) are available in some regions (mazowieckie, podlaskie, warmińsko-mazurskie, lubelskie, pomorskie, kujawsko-pomorskie, wielkopolskie and lubuskie provinces, around 60% of the Polish population) through a Ministry of Health financed programme (till 2014).

Genetic testing

There are about 35 laboratories (public and non-profit) offering testing for rare diseases. Most of them follow external quality control assessments. Diagnostic procedures which are performed in these labs mainly concentrate 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).

There is also possibility of performing testing abroad. If a specific disease is not diagnosed in Poland the National Health Fund may cover such diagnostic procedures, however the regional consultant in genetics must give their approval for such a demand.

Diagnostic tests are registered as available in Poland for 182 genes and an estimated 213 diseases in the Orphanet database²⁹⁷.

National alliances of patient organisations and patient representation

The National Forum for the Therapy of Rare Diseases – ORPHAN, created in 2005, serves as national alliance for rare disease patients' organisations in Poland. As the umbrella of rare disease associations, the Forum groups together the 22 rare diseases patient organisations and it strengthens the cooperation of rare disease patient organisations at the national level. In autumn 2011 the representative of the National Forum was appointed by Minister of Health as the member of the ministerial Rare Disease Task Force, representing the single

²⁹⁶ The list of parties involved in the preparation of the systemic assumptions as well as results of their common work may be reached at www.rzadkiechoroby.pl

³ Information extracted from the Orphanet database (September 2011).

unanimous voice and position of Polish rare diseases patient organisations. More information about the goals, membership and activities of The National Forum for the Therapy of Rare Diseases are published online²⁹⁸.

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 which in 2010 was 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 website²⁹⁹. In order to improve access to information on rare diseases, orphan medicinal products and Orphan 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. All this information is available on the Orphanet website.

Official information centre for rare diseases

There is no official information centre on rare diseases in Poland other than Orphanet.

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 2011

In Poland, Rare Disease Day 2011 was marked by an event at the famous King's Palace on the lake in Lazienki Park in Warsaw. The Organising Committee, created for the event, consisted of 16 Polish rare diseases patients' support groups who created a web page (www.dzienchorobrzadkich.pl) and a Facebook page for the Polish Rare Disease Day. Altogether over 150 people took part: patients, their families and friends, health professionals, parliament and Ministry of Health representatives, the Orphanet-Poland coordinator and the media attended this meeting. The Minister of Health Ms. Ewa Kopacz gave a welcome address and she then presented the government plans for dealing with the issue of rare diseases at national level. The participants heard about help which should be provided for all affected families, the national strategy for rare diseases, intensive work in this field starting this year and Orphanet activities. After an official session, consisting of a few important speeches by the hosts, all of the participants went outside where many white balloons with the Rare Disease Day logo were released. A private 'wish list' was attached to the string of each balloon. Copies of these wishes were given to the Minister of Health as the patients' petition to the Polish government. The event was reported on in the press, local radio, national radio and TV with a number of interviews and talks.

²⁹⁸ www.rzadkiechoroby.pl/np

²⁹⁹ www.orpha.net/national/PL-PL

On 7-8 December 2011 the conference "Partnership for the National Plan for Rare Diseases" was held in Warsaw. This meeting was organised by "Orphan", the National Forum for Rare Disease Therapy, with participation from representatives of the Ministry of Health, families, patient societies, clinical experts, and the Children's Memorial Health Institute's (CMHI) group on rare diseases. The conference was a symbolic, official launch of the work toward developing and adopting a National Plan for Rare Diseases, based on a formula of social consultations. During the first day the current state of Polish patients with rare diseases (RDs) was discussed. The second day took place in the CMHI with the participation of the patient group representatives and the clinical experts who work with rare diseases. The main aim of the discussion was the exchange of experiences and views on the care and treatment of patients and the creation of working-groups, including clinical experts from the Polish reference centers. It was agreed that a patient's input to the draft concerning a National Plan on Rare Diseases will be prepared by the end of February 2012, based on data from the working-groups, and in accordance with the Europlan project. The draft will encompass different areas and aspects of rare diseases, such as classification; diagnostics; medical care; integrated social support; and information and education. Once prepared, the document will be presented to the Polish Ministry of Health for further discussion. On 20 October 2011 a working meeting took place in Warsaw with the participation of the representatives of European paediatric oncology centres and the Ministers of Health of the European countries. It was dedicated to the care of children with cancer, which are all rare diseases. Among other issues, the participants discussed problems related to the establishment of the European Standards of Care for Children with Cancer. The conference was organised by the Polish Ministry of Health in cooperation with the European Society for Paediatric Oncology (SIOPE) in Brussels, and in relation to the Ministry's participation in the European Partnership for Action Against Cancer.

Other rare disease related events included a Dysmorphology meeting in the Children's Memorial Health Institute (Warsaw, 7 June 2011 and Lublin 14 October 2011), V Polish Conference on the Problems of diagnosis, rehabilitation and development of a disabled child", Lublin (13-15 October 2011), "Advances of genetics in pediatric medicine" Course, Warsaw (30 November - 2 December 2011).

Hosted rare disease events in 2011

The following events have been hosted by Poland in 2011: 4th conference of the Eastern European Metabolic Academy (EEMA), Warsaw (26-27 September 2011).

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 is 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.

Participation in European research projects

Polish teams also participate/participated in European rare disease research projects including: EUROGLYCANET, ERNDIM, EUROCARE-CF, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROSCA, EURADRENAL, EURO-GENE-SCAN, MYELINET, NEURO.GSK3, NEUPROCF, RD PLATFORM, TB PAN-NET and SIOPEN-R-NET.

E-Rare

Poland is an observer of the E-Rare 2 project.

IRDiRC

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

Orphan medicinal products

Orphan medicinal product committee

There is currently no orphan medicinal product committee in Poland. For details please refer to the section on national plans.

Accordingly to the new Reimbursement Act (in force since July 2011), the Economic 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 2011, treatment with the following orphan medicinal products has been reimbursed: Cerezyme, Naglazyme, Elapraze, Laronidase and Myozyme (partially)

Specific information on availability of these orphan medicinal products (i.e. number of orphan medicinal products commercialised in 2011) are not available. Information on reimbursement procedures is detailed below.

Orphan medicinal product pricing policy

The Ministries of Health and of Finance decide on maximum public prices and reimbursement status on the opinion of the Medicines Management Team and a HTA recommendation from the Agency for Medical Technology Evaluations³⁰⁰. However, following the implementation of the new Reimbursement Act (July 2011), a few changes have been introduced complying with Transparency Directive. The Medicines Management Team was disbanded and the new Economic Committee takes responsibility in the negotiation process. In addition to this, the role of HTA has been strengthened.

Orphan medicinal product reimbursement policy

At the moment reimbursement of drugs in outpatient settings is based on a reasoned application of the market authorisation holder. Reimbursement of drugs in hospitals is decided through the special procedure initiated by the Minister of Health (requiring a recommendation of the President of the Agency for Health Technology Assessment in Poland).

The abovementioned system will change from 1 January 2012 according to the Act of 12 May 2011 on reimbursement of drugs (in force since July 2011), foods for special dietary use and medical devices. The new system will be unified, application based. The Minister of Health will not be able to introduce reimbursement of a new drug without prior application from the marketing authorisation holder. The application will have to contain among others HTA analyses, information on reimbursement status and pricing in other EU Member States.

Currently, drugs for some rare diseases are reimbursed through therapeutic programmes. Each year the National health Fund selects a priority list for funding through this mechanism: to be included orphan medicinal products must show budget impact and clinical effectiveness³⁰¹. Diseases currently covered include Crohn disease, Prader-Willi syndrome, cystic fibrosis). Five drugs for ultra rare diseases are reimbursed for patients with Gaucher, MPS I, II and VI, and Pompe disease. However, in 2009, Ministry of Health decided to limit the existing available therapy for Pompe disease due to lack of proven clinical effectiveness. Unfortunately, regardless of the new clinical data proving the effectiveness are available since May 2010 and after many interventions made by patient community and physicians the newly diagnosed late on-set Pompe patients do not qualify for the therapy reimbursement as the National Health Fund as well as Ministry of Health were not willing to consider the change of this unjustified limitation. This has led to unequal treatment of citizens, when people diagnosed before 2009 have reimbursement granted as compared with those patients diagnosed after the changes to the therapeutic programme.

The Minister of Health issues a regulation containing a list of chronic diseases for which some drugs are available in pharmacies free of charge, for a flat-rate or partial co-payment. This list includes among others epidermolysis bullosa, phenylketonuria and amyotrophic lateral sclerosis.

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.

Orphan devices

Orphan devices are regularly presented during dysmorphological meetings, national conferences and trainings.

⁴ *Orphan drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011) p 113

⁵ *Orphan drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011) p 114

Specialised social services

There are no social services designed specifically 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 finances 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 12, 2008 the Portuguese Minister of Health approved the National Plan for Rare Diseases (*“Programa Nacional para as Doenças Raras”*).

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 provided healthcare to those people.

Those objectives will be achieved by establishing reference centres for rare diseases, improving the access of patients to adequate care, further improving knowledge and awareness on rare diseases, 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 using 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, a specific tool is already foreseen for the identification of people with rare diseases, aiming at disclosing clinical information to medical doctors and in emergency situations.

The Directorate General of Health, together with the Office of the High Commissioner for Health, have co-funded, in a total amount of €1.9 million, during the years of 2008 to 2011, a few projects on rare diseases, which are currently being developed by several patient associations, what enabled the implementation of a number of strategies mentioned in the National Plan.

Centres of expertise

There are no officially designated centres of expertise for rare diseases in Portugal. However, the National Plan for Rare Diseases will support the creation of officially recognised “Reference Centres”.

The main priority is the identification at national level of reference centres and its official recognition by the Minister of Health.

Following legislation establishing norms for access to therapies involving enzymatic diseases, the National Institute of Health (*“Instituto Nacional de Saúde Doutor Ricardo Jorge”*) created a national network of treatment centres for these diseases: this programme amounted to €32 million in 2011. A list of enzymatic diseases benefiting from free of charge treatment in public hospitals is available.

Pilot European Reference Networks

Some Portuguese institutions participate, or have participated, in the following European Reference Networks for rare diseases: DYSCERNE, ENERCA, NEUROPED and TAG.

Registries

Presently there is a total of 21 registries in Portugal: 16 are from public entities, 4 belong to scientific societies and 1 is from a private institution. In 2011 the Portuguese Registry of Paramyloidosis was officially established by Order nº 8812/2011 dated 2 June 2011.

Upon their own initiative, many patients are also included in international registries or initiatives. A few Portuguese institutions also participate, or have participated, in European registries, such as, E-IMD, TREAT-NMD, EURO CARE CF, EURO CAT, EBAR, SCNIR, CHS, SPATAX, and EUROWILSON.

Neonatal screening policy

The National Programme of Early Diagnosis (*“Programa Nacional de Diagnóstico Precoce”*) started in 1979 at the Institute of Medical Genetics, and initially, it included only the screening of the phenylketonuria. Nowadays, this neonatal screening programme covers almost 98-99% of children born in Portugal and it screens 24 inherited metabolic diseases, as well as congenital hypothyroidism. The screening is made at the Institute of Medical Genetics, the only institution performing this test in Portugal. There are 5 treatment centres to assist patients with congenital hypothyroidism and 9 centres to assist patients with inherited metabolic diseases.

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 293 genes and an estimated 328 diseases, in the Orphanet database³⁰².

Genetic tests are carried out by genetic laboratories within the National Health System, as for instance the National Institute for Health (*“Instituto Nacional de Saúde Doutor Ricardo Jorge”*)³⁰³, as well as in those laboratories located or associated with the five medical genetics services in public hospitals, laboratories in other services in public hospitals (e.g., IPOs – Portuguese Institutes of Oncology) and in private labs. There is also an unknown number of labs offering genetic testing services at universities and research institutions (usually on just one or a few rare diseases). There are five main private labs in Portugal responsible together for a considerable volume of the genetic testing performed in the country.

From 2006 to 2011, in the scope of medical assistance abroad, and as regards rare diseases diagnosis or its confirmation, a total of 1702 clinical cases were sent for referral to foreign centres, 70% of which for molecular study and 30% for laboratorial testing. In 2011, the number of clinical cases sent abroad for referral amounted to 374 situations. From 2006 up to 2011 an increase of 50% has been registered. In 2011 the total expenditure supported by our National Health Service (NHS) was €400 000.

When it is necessary to have a test that is not carried out by a laboratory in Portugal, there is a formal procedure to do that test abroad. Because some public hospitals have legal autonomy, like enterprises, they have contracts with public or private laboratories to make available the exams they need for clinical care.

Genetic testing in Portugal is regulated mainly by Law n.º 12/2005, of 26 January 2005. This Law defines genetic information as the health information linked to the genetic characteristics of one or more related persons (excluding, for its purposes, identity and forensic testing, as well as somatic mutations), obtained through any means, including molecular genetic, cytogenetic, biochemical, physiological tests or imaging, and family history.

Genetic information is considered to be medical information only when used for the confirmation or exclusion of a clinical diagnosis, in prenatal or pre-implantation diagnosis or for pharmacogenetics purposes, thus excluding pre-symptomatic, carrier (for recessive diseases) and genetic susceptibility testing. Only information with immediate interest for the patient’s current status of health (diagnostic and pharmacogenetic information) can be entered in general hospital records; information from pre-symptomatic, carrier, susceptibility, prenatal, pre-implantation forensic and identity testing can only be registered in records of genetic services that must keep separate files (and cannot be accessed by other professionals of the same or of other health institutions, if not involved in the care of those persons).

Diagnostic or pharmacogenetic testing follows the general principles of all other health care intervention. Carrier, pre-symptomatic and genetic susceptibility testing should be preceded by genetic counselling and written informed consent, and requested through a medical geneticist. Pre-symptomatic, susceptibility and pre-implantation diagnosis should only be performed in persons that can fully appreciate all their implications and give their consent. In case of risk for a severe, late-onset disease that has no effective treatment, any predictive testing should be preceded by a psychosocial evaluation and followed after result delivery.

Insurance companies cannot ask for a genetic test or use any kind of genetic information already available (including pedigree information) to refuse life or health insurance or establish a higher premium.

³⁰² Information extracted from the Orphanet database (September 2011).

³⁰³ <http://www.insa.pt/sites/INSA/Portugues/AreasCientificas/Genetica/Paginas/LaboratorioDeReferencia.aspx>

Employers cannot ask for or use any kind of genetic information, even with the workers' consent, except for their health protection (in case of hazardous environments), and only if done in the context of genetic counselling and if their employment is not put at risk; the exception could be made in case of serious risk to public security or public health, in which case genetic testing should be conducted by an independent entity. No genetic testing or any kind of genetic information can be requested in case of adoption, both to the adoptees or the prospective parents. In the case of minors, genetic testing should be done only in their benefit, after written consent from their parents or legal tutors, but also procuring the minors consent.

In case of severe and untreatable diseases, with onset usually in adult life, predictive testing cannot be performed in minors; and prenatal testing should not be done just for information of the parents, but only with the aim to prevent the birth of an affected child. Termination of pregnancy is legal for genetic reasons within the first 24 weeks, and up to term in case of early lethality, e.g., anencephaly.

In case of population studies that may be representative of the whole population or groups of the population, community consent should also be obtained, in addition to the individual consent. In the first case, a specific authorisation of the National Parliament is also needed.

Collection, conservation and usage of biological samples for genetic testing should be subject to informed consent, separate for health care and biomedical research, and that must include its purposes and duration of storage. If consent for a different purpose cannot be obtained, e.g. in case of death, stored samples can be used in the context of genetic counselling, in order to enable treatment or the prevention of a genetic disease in a relative (but not to know the genetic status of other family members). Biological samples cannot be used for any commercial purposes; commercial entities cannot store or use identified or identifiable samples; if absolutely needed, coded samples can be used, if the identifying codes are kept in a public institution.

A biobank is defined as any collection of biological samples or its derivatives, previously accumulated or prospectively performed, obtained through health care provision, population screening or research, with or without any identification, and with or without a time limit. Previous authorization must be requested from the health authorities and, in case of identified or identifiable data, from the Portuguese Data Protection Authority ("*Comissão Nacional de Protecção de Dados – CNPD*"³⁰⁴), the national personal data protection agency. A biobank must have a health care or a (basic or applied) health research purpose; if communication of results can be foreseen, a medical geneticist must be involved.

The Law defines a genetic database as any register, either in an informatics support or not, containing genetic information on persons or families; if a database or a genetic registry includes any kind of family information it must be curated by a medical geneticist.

Some aspects of this Law (as licensing and quality assurance of laboratories, adoption and reimbursement of genetic tests within the national health system, and direct marketing and selling to the public) are still waiting a governmental regulatory decree since 2005.

As a member of OECD, Portugal is, however, subject to the OECD Best Practice Guidelines for Molecular Genetic Testing, and has 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*")³⁰⁵ and APADR – Portuguese Alliance of Rare Diseases Associations ("*Aliança Portuguesa de Associações de Doenças Raras*").

In 2011, FEDRA organized a Conference on "Patients, research and health policies". FEDRA also launched in 2011 the third volume of the publication "Rare Diseases from A to Z", with the collaboration of 36 experts who have reported on around 41 rare diseases, and prefaced by the Director General of Health.

APADR was officially established in 2009, and since then, has developed several action and activities with the aim of improving Portuguese health policy in the field of rare diseases, and further raising awareness to this problem.

Patient organisations were also involved in the public discussion of the National Plan for Rare Diseases. A project has been launched by the Coordinating Commission for the Plan on Rare Diseases ("*Comissão Coordenadora do Programa Nacional das Doenças Raras*") in order to promote regular discussions with patient organisations, especially, with a view to incorporate the needs of these patients into the National Plan.

³⁰⁴ Portuguese Data Protection Authority www.cnpd.pt

³⁰⁵ www.fedra.pt

Sources of information on rare diseases and national help lines

Orphanet activity in Portugal

Since 2003, there is a dedicated Orphanet team in Portugal, currently hosted at IBMC – Institute of Molecular and Cell Biology, Porto.

The team is in charge of collecting data on rare diseases-related services (specialised clinics, medical laboratories, ongoing research projects and clinical trials, registries and patient organisations) in the country, for entry into the Orphanet database. The Orphanet-Portugal team also created and maintains the Orphanet Portugal national website³⁰⁶.

Orphanet is referenced in the National Plan for Rare Diseases as the main source of information regarding activities related to rare diseases in Portugal. Though the support to its activities was specifically mentioned in the Program, the Orphanet Portugal team was relaunched and relocated, after a few years of inactivity, but received no support from the Program or other national sources until 2011.

In June 2010, plans were discussed for co-funding of Orphanet-Portugal's local activities through periodical grant calls from the Directorate General of Health, together with the partnership with the National Plan for Rare Diseases. So far, 148 abstracts were already validated and became available, increasing by more than 50% the number abstracts available in Portuguese in the Orphanet website.

An official event, with media coverage, was held on 26 February 2011 to announce the launch of the Orphanet website in Portuguese, as well as the constitution of the new Scientific Advisory Board. This took place during the conference "Rare but Equal" ("*Raros mas Iguais*"), organised by the APADR in collaboration and with the support of Orphanet-PT, with the presence of the Minister and Secretary of Health, the President of INFARMED (National Authority of Medicines and Health Products), and other health authorities.

In 2011, the Orphanet Portugal team created a Facebook page called "The Orphanet in portuguese" ("*A Orphanet em português*"), hoping that it will become a forum for discussion among all Portuguese-speaking professionals, patients and their organisations, and that it will serve to promote Orphanet in their respective countries. It has already proved useful in helping finding expert volunteers for translations/validations of disease abstracts. In addition, the national team manages a considerable number of questions and inquiries, sent by users mostly by email, requesting information or help.

Orphanet-Portugal has established several partnerships³⁰⁷ with APADR and the Centre for Social Studies, of the University of Coimbra, to update a validated list of Portuguese patient associations; with ACSS (Central Administration of the Health System); with INFARMED for monthly updates of the information on approved clinical trials in the context of rare diseases and of orphan medicinal products available in the country; and with NEDR (Group for the study of rare diseases at the Portuguese Society of Internal Medicine). The final contacts were also made with FCT (Foundation for Science and Technology, the major research funding agency in Portugal), for updating lists of ongoing research projects in Portugal in the field of rare diseases ("rare disease" and the respective "ORPHA number(s)", must be entered as keywords in any new applications for projects dealing with rare diseases). Other partnerships have been entered into with the CEIC (National Ethics Committee for Clinical Research), Calouste Gulbenkian Foundation, Ordem dos Médicos (National Medical Association) and "*Ciência Viva*" (Agency for public science dissemination).

Official information centre for rare diseases

Orphanet is referenced in the National Plan for Rare Diseases as the main source of information regarding activities related to rare diseases in Portugal.

Help line

With funding from the Directorate-General of Health, a call centre was implemented in 2009. The patient organisation RARÍSSIMAS was funded by the Directorate-General of Health in 2008. This help line called "Rare Line" ("*Linha Rara*")³⁰⁸ received almost 2000 information requests (69% by email) in 2011.

The Portuguese Haemophilia Association also provides some support by phone. Several other patient associations have a helpline or provide help online or by email.

The Orphanet-Portugal team also deals with many requests for information from patients coming Portuguese-speaking countries.

³⁰⁷ An updated list of all partnerships can be consulted at www.orpha.net/national/PT-PT/index/parcerias.

³⁰⁸ www.linharara.pt

Other sources of information on rare diseases

The APPDH – Portuguese Association of Parents and Patients with haemoglobinopathies (“APPDH - Associação Portuguesa de Pais e Doentes com Hemoglobinopatias”), member of APADR, published 3 mini-books about haemoglobinopathies, mainly for children, but also useful for adults.

The APN – Portuguese Association of Neuromuscular Diseases (“Associação Portuguesa de Doenças Neuromusculares”) a member of APADR as well, published, in 2011, 2 booklets: “Neuromuscular Diseases Manual: for healthcare professionals” (“Manual sobre Doenças Neuromusculares: Técnicos e Profissionais de Saúde”) and “Neuromuscular Diseases Manual: for patients and caregivers” (“Manual sobre Doenças Neuromusculares em Idade Pediátrica: Doentes e Cuidadores”).

Good practice guidelines

Although this is the formal role of the Portuguese Medical Association (“Ordem dos Médicos”), the tradition in Portugal has been mainly to follow well-established and internationally respected best practice guidelines, rather than developing new ones, except for some specific contexts (as is the case with protocol for presymptomatic testing and genetic counselling in late-onset neurological disorders or some metabolic hereditary diseases).

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 Testing³⁰⁹ led the process of defining the EMQN BP Guidelines for the Molecular Genetic Testing in the SCAs (dominant ataxias)³¹⁰, 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. The first six genetic counsellors graduated in 2011.

In July 2011, during the post-graduation course “Mental Retardation: from Clinic to Gene and Back” (2nd Edition)³¹¹ a session was about Orphanet services was presented. The audience included molecular and clinical geneticists as well as post-graduation students.

Some patient associations have organised one-day receptions for medical students, so that they are made aware of rare diseases and rare disease patients. Some also organise voluntary rotations for other health professionals, such as social workers and speech therapists.

National rare disease events in 2011

To mark the Rare Disease Day 2011, the Portuguese Alliance of Patients Associations of Rare Disorders (APADR), in collaboration with Orphanet-Portugal, organised a conference on the theme “Rare but Equal”, on 26 February 2011. Patients, families, patient associations’ representatives, industry representatives, policy makers and health authorities (including the Portuguese Ministry of Health and the Secretary of State for Health, the Vice-Director of Directorate-General of Health, the Social Security Director and the President of INFARMED - the National Authority for Drugs and Health Products), health professionals and researchers and several members of the Scientific Advisory Board of Orphanet-Portugal were present. The Ministry of Health

³⁰⁹ www.oecd.org/dataoecd/43/6/38839788.pdf

³¹⁰ www.eurogentest.org/uploads/1283847353000/SCABestPracticeGuidelines-WebsiteVersion.pdf

³¹¹ <http://www.icvs.uminho.pt/postgraduation/MentalRetardation/default.aspx>

recognised officially the importance of Orphanet activities. Both FEDRA (in Lisbon) and APADR (in Porto) hosted Rare Disease Day events in 2011.

On 11-12 March 2011, the Second Symposium of the *NERD* of the Portuguese Society of Internal Medicine was held in Tomar: the proposed development of a National Registry of Rare Diseases was discussed.

On 10-12 November 2011, the 15th Annual Meeting of the Portuguese Society of Human Genetics was held in Lisbon, with a communication and poster about rare diseases and Orphanet.

Hosted rare disease events in 2011

Amongst the hosted events announced in *OrphaNews Europe* in 2011 were: the 3rd European Phenylketonuria Group Symposium - Advances and challenges in PKU (24-26 March, Lisbon), the Eighth European Cytogenetics Conference (2-5 July 2011, Porto), the 13th International Conference on Chronic Myeloid Leukemia: Biology and Therapy (September 2011, Estoril), and the European Congress on Myocardial and Pericardial Diseases (13-15 October 2011, Lisbon).

Research activities and E-Rare partnership

National research activities

The public funding agency, Foundation for Science and Technology (FCT), runs several programmes to fund research on rare diseases, as well as the Ministry of Health itself and the private sector.

Participation in European research projects

Portugal participates, or has participated, in European rare disease research projects including: CLINIGENE, EPOKS, Euro-WILSON, SPATAX, EURAMY, EURO CARE CF, EuroGentest-2, EVI-GENORET, LEISHMED, MMR-RELATED CANCER, NEUPROCF, PEROXISOMES, POLYALA, RHORCOD, SAFE, PHGEN, RIBERMOV and SIOPEN-R-NET

E-Rare

Portugal is represented by FCT and the Directorate-General of Health, joined the E-Rare project in 2009, for the 2nd Joint Transnational Call: Portugal is represented by a team in one of the projects/consortia selected for funding, with a funding of around €200,000. Portugal did not join the 3rd Joint Transnational Call in 2011.

IRDiRC

Portuguese funding agencies are not currently committed members of the IRDiRC.

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 for a monthly update on all the orphan medicinal products approved and available in the country.

Orphan medicinal product committee

There is no such committee in Portugal

Orphan medicinal product incentives

No specific incentives are currently in place.

Orphan medicinal product market availability situation

A list of orphan medicinal products launched on the market in Portugal³¹² is published on the Orphanet Portugal entry site to the Orphanet database. This data is provided by *INFARMED* and is regularly updated.

Orphan medicinal product pricing policy

Orphan medicinal product pricing policy fall under the responsibility of the Ministry of Health.

Orphan medicinal product reimbursement policy

All Portuguese citizens are covered by the National Health Service, although they may have to participate towards the payment of prescription drugs. There are special programmes in place to facilitate access to growth hormone therapy and enzymatic therapy.

³¹² <http://www.orpha.net/national/PT-PT/index/lista-de-medicamentos-órfãos-disponíveis-em-portugal/>

The investment of the NHS in orphan medicinal products in 2011 exceeded €83 million, which represents 8.2% of the total consumption of medicines in hospitals. It should be noted that there was an increase of 15.4% in this group of drugs, as compared to 2010. It must be kept in mind that the total increase in hospital spending in 2011 grew only 1.3%, compared to 2010, when including orphan medicinal products. It must be noted also that 5 orphan medicinal products account for 60% of expenditures in this group (Imatinib, Bosentan, Galsulfase, Lenalidomide, dastinib)³¹³. Regardless of its condition of use and supply in Portugal, and the status of its current assessment prior to use, all patients within the existing criteria and procedures (e.g. SUA) will have access to 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 (see section on “Orphan medicinal product availability”). If an authorised orphan medicinal product is not commercialised in Portugal, but marked in other Member States, the treating hospital can request special authorisation from INFARMED: if use is approved, the hospital is directly supplied by the manufacturer, and there is no co-payment from the patient³¹⁴.

Orphan devices

Orphan devices also fall under the responsibility of INFARMED.

Specialised social services

Respite care services exist, both in the public, private and social sector, and patients must pay for some services. Other respite facilities are run by patient organisations and some projects have been established with public support. Raríssimas is building a care centre for patients with rare diseases, the construction of which started in July 2010.

Raríssimas has two multidisciplinary centres, which will 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.

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

³¹³ Source: Consumo de Medicamentos em Meio Hospitalar - Dezembro 2011

http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ANALISE_MENSAL_MERCADO/ANALISE_MERCADO_MEDICAMENTOS_CHNM/2011

³¹⁴ *EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, C. Habl, F. Bachner (2011), p57

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 Government³¹⁵ (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), 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
 - x. Bulous epidermolysis
 - xi. Prader Willi syndrome
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.

Four meetings of the National Committee for Rare Diseases were organised in 2011. In July 2011 the Romanian Association for Rare Cancers was established and at the National Committee for Rare Diseases meeting in November 2011 rare cancers were included in the proposal for the National Plan for Rare Diseases. The EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases were also discussed and most have been included in the content of the Romanian National Plan 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:

³¹⁵ <http://www.ms.ro/?pag=133>

- 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.

In terms of funding and governmental support, in July 2011 the budget allocation for National Program for Rare Diseases was increased by €2,000,000: 43 more patients affected by rare diseases were included in the program (7 patients with Hunter Syndrome, 3 patients with Harley Syndrome, 1 patient with Congenital Afibrinogenemia and 33 patients with congenital primary immunodeficiency).

On 28 June 2011 the official opening of the Pilot Reference Centre for Rare Diseases took place in Zalau (see section entitled "Centres of expertise"). Romania marked an important advance in services provided to Romanian rare disease patients. The Minister of Health allocated a financial support for the new Pilot Centre, amounting to €80,000.

Centres of expertise

There are no official centres of expertise in Rare Diseases in Romania at the moment, and 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.

In the view of Romanian Ministry of Health, expertise has developed around the medical Universities and currently many rare diseases are diagnosed and treated. The Operative Commission of Rare Disease recently 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. In 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 common registry of Rare Diseases was also proposed to be implemented in every Centre of Expertise based on the existing database for different rare diseases, with a deadline in 2013.

The official opening of the Pilot Reference Center for Rare Diseases "NoRo" took place on 28 June 2011 in Zalau. The establishment of the NoRo Center was 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 involved

11 partners: Romanian Prader Willi Association (main applicant), Norwegian Prader Willi Association, Frambu - Norwegian Center for Rare Diseases, Ministry Health Romania, 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 opening event was attended by Mrs. Minister of Health and Care Services Norway Anne-Grete Strom-Erichsen, Mr. Minister of Health Romania Cseke Attila, Mr. Ambassador of Norway in Romania Oystein Hovdkinn, Director of the Norwegian Cooperation Programme in Romania and Bulgaria Tore Lasse By, representatives of EURORDIS, Orphanet Romania and patients' associations from Hungary, Italy, France, Denmark, Spain, Norway, Bulgaria, Russia, Sweden, the Secretary General of the Second National Plan for Rare Diseases France, local officials and members of EUCERD. Also was present Mr. Bercea Virgil, Greek Catholic Bishopric of Oradea, who officiated the holy ceremony of the opening.

In addition an International Conference entitled "The European approach for rare diseases" was held on 29 June 2011, in Zalau to mark the official opening of the first Pilot Reference Centre for Rare Diseases in Romania. The Romanian Prader Willi Association and Romanian National Alliance for Rare Diseases organised the event. This event was based around the theme of quality care, the empowerment of patients and families and the examples of the Frambu model and the French National Plan for Rare Diseases. The program included two roundtables around the themes "Addressing the needs of patients" and "Innovation in the field of rare diseases." The 92 participants included representatives of the rare diseases centres around Europe were present (i.e. Norway's Frambu, Sweden's Agrenska, Spain's CREER, Hungary's Centre for Rare Diseases).

Pilot European Reference Networks

Romanian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, TAG and Care-NMD.

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 Government³¹⁶ 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.

There are currently a number of patients' registries in Romania in the field of rare diseases including: the 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.

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: EURO CARE CF and the European Registry for CML (EUTOS).

³¹⁶<http://www.ms.ro/?pag=133>

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).

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 2011 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 at national level as having specific expertise in the field. Private laboratories offer a variety of modern molecular tests for purchase.

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 so 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 29 genes and an estimated 26 diseases in the Orphanet database³¹⁷.

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.

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.

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

³¹⁷ Information extracted from the Orphanet database (May 2011).

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.

Official information centre for rare diseases

The Romanian Prader Willi Association established an Information Centre for Rare Genetic Diseases in 2005³¹⁸, 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 as well as training. 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.

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 is in development. At the end of 2011 the scientific advisory board was renewed and forms have been sent to specialists to update information available/introduce new information.

Official information centre for rare diseases

The Romanian Prader Willi Association established an Information Centre for Rare Genetic Diseases in 2005, providing information³¹⁹ 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 as well as training. The activities are financed by different projects and the service is accredited by the Ministry of Labour.

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.

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 Diseases³²⁰” 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.

³¹⁸ http://www.apwromania.ro/oamenirari/ghid_servicii_en/index.html

³¹⁹ http://www.apwromania.ro/oamenirari/ghid_servicii_en/index.html

³²⁰ www.rjrd.ro

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.

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.

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)³²¹ 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 have been elaborated and the training courses were due to start once the Pilot Reference Centre for Rare Diseases "NoRo" opened in 2011.

National rare disease events in 2011

The Romanian National Alliance for Rare Diseases marked Rare Disease Day with events organised by member organisations in Bucharest, Timisoara, Cluj-Napoca, Iasi, Zalau, Targu Mures and Oradea³²². Celebrated under the slogan "Rare, but Equal", the aim of the day was to raise awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives.

The Rare Diseases Day campaign in Romania was a success and captured the attention of all institutions. Around 1000 participants took part in the events in the 3 main towns, six conferences, and a press and TV campaign. The theme of 2011 Rare Disease Day was a good way to support efforts to advocate at the Ministry of Health for the Romanian National Plan for Rare Diseases to be included in the National Strategy for Public Health.

The media coverage of Rare Disease Day in Romania was greater than usual. Coverage included a serial about patients' lives in the national newspaper, several documentaries presenting the everyday life of patients, and various other TV programs and reports in national newspapers. On 24 February 2011, "Carol Davila" University of Medicine and Pharmacy hosted a conference for both professionals and patients which

³²¹ www.edubolirare.ro

³²² <http://ziubolilorrare.wordpress.com>

revealed the gaps in health that exist for rare disease patients between and within countries and gaps in health that exist for rare disease patients compared to others in society. This national event in Bucharest included the participation of representatives from Ministry of Health, National Drug Agency, Romanian Genetics Society, National Doctors Collegiums' was accompanied by a press conference and was well covered in the press and on TV. A booklet entitled "Rare Inequal" was published with patients' stories, which had a great impact.

On 5 March 2011, the University of Medicine and Pharmacy Iasi and Orphanet Romania organised events in connection with Rare Disease Day in Iasi.

At the National Conference of Thrombosis and Haemostasis in November 2011, a special workshop about rare diseases in field of thrombosis and hemostasis was held.

Hosted rare disease events in 2011

No rare diseases events hosted by Romania were announced in 2011 by *OrphaNews Europe*.

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 2011 there was a general call for projects (non-rare disease specific), which is still under evaluation. 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.

E-Rare

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

IRDiRC

Romanian funding agencies are not currently committed members of 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 is available on the website of the Romanian National Medicines' Agency³²³ and includes: Aldurazyme, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyr, 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, Thromboreductin, Torisel, Tracleer, Trisenox, Ventavis, Volibris, Wilzin, Xagrid, Xyrem, Yondelis, Zavesca.

Orphan medicinal product pricing policy

No specific information reported.

³²³ <http://www.anm.ro/ /Lista%20medicamentelor%20orfane%20valide%20in%20Romania.xls>

Orphan medicinal product reimbursement policy

The National Programme for Rare Diseases provides for the reimbursement of 17 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.

Orphan devices

No information reported yet.

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.

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

No national plan or strategy for rare diseases currently exists in Slovak Republic and there is no specific budget currently dedicated to rare diseases. However, a working group was established in January 2011 at the Ministry of Health and work has begun on a “Strategy for improving health care for patients with rare diseases”. This document is being reviewed at the Ministry of Health level. A workshop was also held in December 2011 concerning rare diseases at the Ministry of Health.

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 metabolism or specialised outpatient clinics, as well as in cooperation with some research laboratories of Slovak Academy of Science. A small workshop was held in December 2011 concerning rare diseases at the Ministry of Health and this group is now working on the criteria for centres of expertise in line with those issued by the EUCERD. Several specialised and centralised departments would be appointed as centres of expertise in the near future (e.g. oncogenetics, hereditary metabolic diseases).

Pilot European Reference Networks

Teams from the Slovak Republic participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne.

Registries

At present, there is no national committee dedicated to dealing with registries and no national rare disease registry. 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 are: the National registry for congenital disorders (established in 1976), the National registry for congenital heart defects (established in 1992), the National cancer and rare cancers registry (established in 1976), 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. national registry of haemophilia).

The Slovak Republic contributes to the European Cystic Fibrosis Society Patient 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 hypothyreosis (CH), 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 disorder, 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. 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 3-5 bigger and several smaller DNA laboratories which perform molecular diagnostics for around 350 monogenic mendelian disorders. There are currently no reference laboratories in Slovak Republic. National guidelines for genetic testing have not yet been approved, but are being developed at national level. Slovak Republic 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. Genetic testing also takes place abroad, mainly in the Czech Republic.

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.

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.

Sources of information on rare diseases and national help lines

Orphanet activities in the Slovak Republic

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 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 launched in 2011 the Orphanet Slovakia national website³²⁴.

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 municipalities.

Good practice guidelines

Best practice guidelines have been developed for cystic fibrosis, maturity-onset diabetes of the young, Wilson disease and haemophilia. 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.

Training and education initiatives

Currently, there are no training or education initiatives organised systematically in the field of rare diseases.

National rare disease events 2011

To mark Rare Disease Day 2011 several events was organised, mainly through mass media presentations. On the website of Slovak Ministry of Health there was a short advertisement about Rare Disease Day. Short films were broadcasted on TV and wider discussions took place on the radio. Several rare diseases related presentations were organised in the context of local medical conferences and seminars.

Izakovic's Memorial is an annual conference organised in Slovak Republic by the Society of Medical Genetics, related to genetic and rare diseases. In 2011 the conference was specially focused on problem of rare diseases.

Hosted rare disease events 2011

The DIABGENE Laboratory from Slovak Academy of Sciences organised from 30 September to 3 October 2011 the meeting "The Genetic of Diabetes in Post-Genome Wide Association Era" devoted to monogenic forms of diabetes and/or hereditary hyperinsulinism.

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 are not currently committed members of 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. The Slovak Ministry of Health is responsible for pricing and reimbursement of all drugs as well as orphan medicinal products.

³²⁴ <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/>

Orphan medicinal product incentives

To attract orphan medicinal products manufacturers 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 a special register for patients with rare diseases could 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. All orphan medicinal products registered at EU level are registered in the Slovak Republic and at the end of 2011 26 orphan medicinal products were on the Slovak market: Myozyme, Fabrazyme, Aldurazyme, Naglazyme, Zavesca, Kuvan, Ventavis, Revolade, Nplate, Firazyf, Volibris, Tracleer, Revatio, Somavert, Increlex, Litak, Glivec, Nexavar, Sprycel, Tyverb, Tasigna, Torisel, Lysodren, Vidaza, Inovelon, Exjade.

The reimbursement level is set in a national process named “categorisation”.

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” of all reimbursed drugs is published every quarter.

At the end of 2011 26 orphan medicinal products (OMP) were on the Slovak market. Out of the 26 OMP, 7 OMP need patients’ participation at their costs (Myozyme, Revolade, Firazyf, Volibris, Somavert, Litak, Inovelon). However some orphan medicinal products are at the market in different packages (example Myozyme 1x50mg, 10x50mg, 25x50mg), and one out of them is fully reimbursed. Indeed Myozyme, Somavert and Litak have a fully reimbursed alternative. The highest copayment was for Myozyme plc ifo 25x 50mg (€287.61). However if we express the copayment as percentage of the total price, the highest copayment was in Somavert plv iol 1x20mg - 36.78%. Somavert has other three alternatives (30x20mg, 30x10mg, 30x15mg) on the Slovak market, which are fully reimbursed. 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”.

Other initiatives to improve access to orphan medicinal products

Only categorised drugs are directly available on the Slovak market. In the case of the drug not being ‘categorised’ the drug can be delivered on named-patient basis. Responsibility for approving delivery on a named-patient basis rests with the Ministry of Health according to Act 140/1998.

Several activities in 2011 stressed the importance of orphan medicinal product availability and to inform care givers, insurers as well as other health care professionals about situation in the Slovak Republic including a seminar in cooperation with State Institute for Drug Control and the Slovak Society for Pharmacoeconomics³²⁵ and a publication written in English on the topic³²⁶. Results of the use of OMP were presented also at 40th Symposium of European Society for Clinical Pharmacy in Dublin (18- 21 October 2011).

Orphan devices

No specific information reported.

³²⁵ <http://www.sukl.sk/sk/o-nas/vzdelavacie-akcie-a-prezentacie/prezentacie-2010/dostupnost-orphan-liekov-v-sr>

³²⁶ Foltánová, T. - Petrová, L. - Mazág, J.: *The need for pricing and reimbursement policy of orphan medicinal products in the Slovak Republic.*

*Foltánová T., Tomáš S., Petrová L., Kuželová M., Káčkošová V.: *How expensive is the treatment of pulmonary arterial hypertension with orphan medicinal products in the Slovak Republic? Connecting Care & Outcomes, 2011. - S. 138*

http://www.fpharm.uniba.sk/fileadmin/user_upload/admin/Acta_facultatis/Tomus_LVII/ACTALVIIIFoltanova.pdf

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 no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

There is currently no national plan for rare diseases in Slovenia and there is no dedicated budget for rare diseases and costs related to rare diseases are covered by the national health care insurance scheme. A working group was created at the Ministry of Health in 2010 which prepared a draft national plan for rare diseases in 2011 which has now passed a professional and lay public consultation phase. The plan³²⁷ was accepted by the Health Council in February 2012 and the next steps will be to elaborate an action plan and its implementation.

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.

Pilot European Reference Networks

Slovenian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, NEUROPED, TAG, Care-NMD and EN-RBD.

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 EURO CARE CF European 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.

³²⁷ http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nact_dela/Nact_dela_na_podrocju_redkih_bolezni.pdf

Diagnostic tests are registered as available in Slovenia for 47 genes and an estimated 50 diseases in the Orphanet database³²⁸.

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 website³²⁹.

Official information centre for rare diseases

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

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

National clinical guidelines are not available.

Training and education initiatives

No specific activity reported.

National rare disease events in 2011

To mark Rare Disease Day, a press conference was organised on 28 February 2011 to raise society's awareness of rare diseases, to inform the general public about rare diseases and to improve cooperation between patients and medical profession for better quality of life of patients. To raise awareness about the rare diseases in Slovenia an article has been written for Wikipedia in the Slovenian language.

Hosted rare disease events in 2011

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.

³²⁸ Information extracted from the Orphanet database (September 2011).

³²⁹ <http://www.orpha.net/national/SI-SL/index/domov/>

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.

E-Rare

Slovenia is not currently a partner of the E-Rare project.

IRDIRC

Slovenian funding agencies are not currently committed members of 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. The Strategic Council for Drugs in 2010 provided additional government budget funds of €1'000'000 to finance two orphan medicinal products for the treatment of two patients with a rare haemolytic condition and to treat one patient with Hunter syndrome. For the year 2011 additional funding was provided for two orphan medicinal products for the treatment of children suffering from acute lymphoblastic anemia (Evoltra) clofarabine and in preparation for bone marrow transplantation (Busilvex) busulfan. Both drugs are already available and in use within the public healthcare system.

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)³³⁰."

Orphan medicinal product market availability situation

The orphan medicinal products launched on the market up to the end of 2011 were: Afintor, Busilvex, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Glivec, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tasigna, Tepadina, Thalidomide, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xyrem, 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.

The following orphan medicinal products were covered (without the need for any co-payment by the patient) by the Health Insurance Institute of Slovenia in 2010: Afinitor, Busilvex, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Glivec, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Replagal, Revatio, Revlimid, Revolade, Savene, Somavert, Sprycel, Sutent, Tasigna, Tepadina, Thalidomide, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xyrem, Zavesca.

In 2010, the public expenditure for orphan medicinal products increased by 26,31%, which is considerably more than the average increase in expenditure for other drugs. In 2010 (the latest data available)

³³⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

900 patients were receiving orphan medicinal products in Slovenia, however, the number of patients in Slovenia with rare diseases is not known at this stage.

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.”³³¹

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.

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). 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. One of the initiatives undertaken by the CISATER led to the creation of the first Spanish Language Rare Diseases Information System (Sistema de Información de ER en español, 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. 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 CIBER on Rare Diseases or CIBERER, a centre attached and funded by the Instituto de Salud Carlos III, 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 patient.

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

³³¹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

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 2009³³². It is set within the framework of the Quality Plan of the Spanish National Health System (NHS) which includes, amongst other objectives, improving care for people with rare diseases and their families. 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. Through this initiative the Spanish Government aims to formulate a feasible and adequate response to the needs of people affected by rare diseases, and the combined efforts of all those involved was fundamental to the achievement of that objective. 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. A rigorous approach to any rare disease calls for a set of actions that establish evidence-based, agreed criteria regarding the guidelines to be followed in any one of the strategy lines set out herein, in order to enhance the effectiveness and quality of the treatment of these pathologies in all the health services of the Spanish health system.

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. This will contribute to an improvement in the quality and outcomes of the services and healthcare provided in the field of rare diseases. 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 Autonomous Communities (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 Autonomous Communities 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. The Ministry of Health, Social Services and Equality uses the *Funds for the Implementation of Health Strategies* in particular: these funds are used by the Autonomous Communities to implement the Rare Diseases Strategy of the Spanish National Health System.

The Europlan Spanish 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 online³³³.

The Strategy was evaluated in 2011 and the results are now to be analysed. This assessment will focus mainly on the implementation of the Strategy over the first two years, although it is too soon to measure quality of life this process could help to update recommendations and objectives.

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

³³² <http://www.msc.es/organizacion/sns/planCalidadSNS/docs/RareDiseases.pdf>

³³³ <http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report Spain %20europlan.pdf>

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 Autonomous 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.).

Several Autonomous Communities have started to map their resources in order to elaborate and inventory of clinical experts, social services, diagnostic laboratories, etc.

Centres of expertise

In Spain, Royal Decree 1302/2006 of 10 November 2006 establishes the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS. It defines the characteristics to be met by pathologies or groups of pathologies 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 of the Spanish NHS, which was created in the aforementioned Royal Decree 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, we are gradually working 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 pathologies 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 procedures for which it is necessary to designate CSUR in the Spanish NHS, as well as, the criteria that these shall be met 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).
- Penetrating keratoplasty in children.
- Children's transplants (kidney, intestine, liver, heart, lung).
- 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.

Once the criteria has been agreed a period of CSUR application is opened, and the Autonomous Communities 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. To date, the Interterritorial Council and the Ministry of Health, Social Services and Equality have agreed to designate 132 CSUR for 35 pathologies or procedures, including some related to rare diseases.

On February 29, 2012 the proposals for designating 34 new CSURs were submitted to the Interterritorial Council. When these new proposals are approved there will exist a total of 166 CSURs of 40 diseases or procedures.

At the same time, work continues in other areas of specialisation to define all the pathologies and procedures, among them those related to rare diseases, which should be carried out in CSUR. In the areas of congenital metabolic diseases and rare neurological disease a work is currently being developed, being already constituted the groups of experts, scheduled to raise their proposals to the Designation Committee of CSUR and the Interterritorial Council in the first half of 2012. During 2011 FEDER (Spanish Federation for Rare Diseases) participated in the CSUR project with regard to rare diseases, by providing professionals to participate in the groups of experts related to rare diseases.

All information concerning the CSUR project is available for health professionals in the Web of the Ministry of Health, Social Services and Equality.

A centre for rare diseases in Burgos, “State Reference Centre for Rare Diseases Patients and their Families” (CREER) was inaugurated on 30 September 2009 by the Spanish Minister 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.

Pilot European Reference Networks

Spanish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPI, EPNET, ENERCA³³⁴, EUOHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma Network, PAAIR and EUROAGENTEST.

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 Rare Diseases Research Institute (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 Rare Diseases Research Institute (IIER), belonging to ISCIII, is currently in charge of this registry. This registry is sustained by government financing at the moment.

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.

³³⁴ <http://www.enerca.org>

At regional level, Extremadura has run a population-based registry on rare diseases since 2004. Andalusia, Castilla-La Mancha, Murcia and Comunitat Valenciana are taking steps to develop their own.

Since December 2011, a project on the “Spanish Rare Disease Registries Research Network” is being carried out and coordinated by IIER; all the Autonomous Communities are participating in the project. The main objective is to develop the National and Regional registries for rare diseases.

Spain also contributes to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, EIMD, EURO-WABB, MOLDIAG-PACA, AIR, 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 almost all Autonomous Communities. Nevertheless, the neonatal screening programme offer differs greatly among different Spanish Autonomous Communities³³⁵: 10 included cystic fibrosis, 5 congenital adrenal hyperplasia, 4 sickle cell disease, 2 biotinidasa deficiency and 1 galactosemia. In addition, 7 Autonomous Communities have extended the newborn screening programme by Tandem Mass Spectrometry.

A working group with representatives from the Ministry of Health, Social Services and Equality, Regional health services and scientific associations, is currently reviewing scientific evidence and will produce a report and recommendations about neonatal screening for the National Health System³³⁶. A previous study was carried out in 2007 by the Public Health Commission of the Interterritorial Council of the Spanish NHS on the situation of newborn screening programmes in Spain, the *Informe sobre la situación de los programas de cribado neonatal en España*³³⁷. 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 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, several Spanish Technology Health Assessment Agencies have been developing report on information to parents about neonatal screening and report criteria for the cost-effectiveness of a neonatal screening programme using Tandem Mass Spectrometry³³⁸.

Genetic testing

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).

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

³³⁵ Source: “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)

³³⁶ 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)

³³⁷ “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)

³³⁸ 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. Avaluat. N.º 2006/07.*

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, several Autonomous Communities, along with the Asociación Española de Genética Humana (AEGH), are mapping the resources related to the genetic testing area.

The Spanish Society of Genetic Counselling (SEAGEN)³³⁹ officially launched in December 2011 with the aim of promoting and developing genetic counselling in Spain. The society expects to bring together Spanish professionals working as genetic counsellors and those interested in the field. The main goals are the promotion and development of the profession in Spain, the implementation of specialised training in the area, and the establishment of collaborations with reference societies in the field from other countries.

Diagnostic tests are registered as available in Spain for 1081 genes for 974 diseases in the Orphanet database³⁴⁰.

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 Policy and Equality).

FEDER is currently developing several specific agreements with CREER in order to improve the collaboration and the empowerment of FEDER patient organisation and has also signed Framework Agreement with CIBERER.

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) y 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 website³⁴¹ in Spanish. 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.

³³⁹ <http://www.seagen.es/>

³⁴⁰ Information extracted from the Orphanet database (September 2011).

³⁴¹ <http://www.orpha.net/national/ES-ES/index/inicio/>

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 Health.

Help line

FEDER's Service of Information and Orientation (SIO) provides a phone and internet helpline which receives support from the Ministry of Health.

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 18'000 consultations since 2000, when it was established with the support of the former Social Affairs Ministry, although it no longer receives Ministry support. The help line 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. Social, legal, psychological support as well as training is provided to individual patients, associations, professionals (and others) by specialised staff (e.g. three social workers and a psychologist). 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/pathology group. The help line belongs to the European Help Lines Network, led by EURORDIS.

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.

A Spanish-language book entitled *Rare diseases, Manual of Humanity* was officially released in Madrid in November 2009. The publication contains twenty-six personal stories of people affected with a rare disease, each of whom describe their situation. The experiences are followed by scientific descriptions of the different diseases concerned, written by clinical specialists. Diseases featured include dermatomyositis, interstitial cystitis/painful bladder syndrome, mitochondrial myopathy, epidermolysis bullosa, Prader-Willi syndrome and more. The Spanish Federation of Rare Diseases (FEDER) was involved in the development of the book, together with publishing house Lo Que No Existe. The publication includes two appendices offering general information on rare diseases and listing patient association contacts in Spain.

A book entitled "Communication strategies and challenges for rare diseases: Medical research as a referent"³⁴² was presented at Rare Disease Day 2011. Social researchers from the Universidad de Almería and Valencia's CEU-Cardenal Herrera University offered, for the first time, a quantitative and discursive analysis of the treatment of rare diseases in the Spanish press over a one-year period. The book, freely downloadable in English and Spanish languages, is intended for students – future researchers, clinicians and journalists- as well as for active professionals in these fields, in addition to patients and patient associations.

Good practice guidelines

Since 2000, *IMSERSO* (the main Spanish Institution in charge of providing social support for disability 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*³⁴³ is a programme which is supported by the Ministry of Health and Social Policy and Equality through the NHS Quality Agency. 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.

³⁴² http://www.ciberer.es/documentos/Libro_Ingles.pdf

³⁴³ <http://www.guiasalud.es/home.asp>

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 (SEMFyC) in Valencia. The protocol, *Protocolo Dice de Atención Primaria de Enfermedades Raras (DICE-APER)* was created by SEMFyC's working group on Clinical Genetics and Rare Diseases³⁴⁴, in collaboration with the 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 Instituto de Investigación de Enfermedades Raras (IIER) (Ethical Committee of the Rare Diseases Research Institute) has published a series of guideline documents regarding registries, biobanks, and neonatal screening³⁴⁵. Originally published as separate articles in the Spanish Health Ministry publication *Revista Española de Salud Pública*³⁴⁶, 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

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'. The second edition started in 2011.

Other initiatives led by CIBERER are the organisation of training courses on rare diseases. Amongst others, CIBERER has organised in 2011 three specific courses on the application of OMICS to rare diseases research, a course on animal models phenotyping and a course intended to health professionals for a general overview of rare diseases.

The Bancaja Foundation and CIBERER and have launched another 'Becas Lanzadera' ("Scholarship Shuttle") to attract the best students to research in the field of rare diseases. These grants a year amounting to €60,000, will enable trainees to work in various research projects in the field of rare diseases (cause birth defects, metabolic disorders, disability, sensorineural disorders and intellectual deficiencies) in order to understand their causes and nature, and to develop diagnostic and therapeutic tools.

During 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.

National rare disease events in 2011

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.

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.

In 2011, FEDER, in collaboration with its more than 200 patient organisations, coordinated the Rare Disease Day Campaign. A number of activities were organised including, the adoption of an official act in the Spanish Senate (Madrid), the 2nd Solidarity race for the rare diseases (Madrid), Multitudinous march, V Orphan

³⁴⁴ <http://dice-aper.semfyc.es/web/index.php>

³⁴⁵ http://www.isciii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf

³⁴⁶ http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm

drugs and Rare Disease Congress (Seville), Solidarity fair and Benefit Dinner (Barcelona), Solidarity race for the Rare Diseases (Badajoz), Cultural activities and race (Murcia), and VII Rare Disease Encounter (Valencia).

On the occasion of the Rare Diseases Day 2011, the III Meeting "To Research is To Advance" was held in Madrid on 23 February 2011, organised by the Centre for Biomedical Network Research on Rare Diseases (CIBERER). The event was attended by over 150 people and included the participation of researchers and patient organization representatives, who gave examples of collaboration between multidisciplinary teams and patients in metabolic diseases, amyotrophic lateral sclerosis and fragile X syndrome. Moreover, the book entitled "Communication strategies and challenges for rare diseases: Medical research as a referent"³⁴⁷ was presented.

Other national events related to rare diseases organised in 2011 included: "Keys for the assistance in primary care on rare diseases Valencia (13 January 2011)", V International Congress of Rare Diseases and Orphan Drugs, Seville (17-19 February 2011), Masters Course "Current knowledge of rare diseases", Seville (11 March 2011), National Congress of Human Genetics, Murcia (30 March-1 April 2011), Genome Spain workshop 2011 "Genomics, proteomics and bioinformatics applied to the study of rare diseases", Malaga (3-4 May 2011), IX Congress of the Spanish Association for the Study of Inborn Errors of Metabolism (AECOM) Valencia (28-30 September 2011), Course on "Rare diseases: research, clinical care and social awareness", Valencia (5 October 2011), II Spanish Biobank Network Congress, Tarragona (20-21 October 2011), VII Annual Conference of the Spanish Association for the Information and the Research of genetic renal diseases (AIRG-E), Barcelona (19 November 2011).

Hosted rare disease events in 2011

Every year since 2000, the Royal College of Pharmacists in Seville has organised the International Congress on Orphan Drugs. Other events announced in *OrphaNews Europe* in 2011 included: 2nd Annual Commercialisation & Market Access Strategies for Orphan & Ultra-Orphan Drugs (17 February 2011, Barcelona), Third International Symposium on Paediatric Movement Disorders (25-26 February 2011, Barcelona), 9th International Prenatal Screening Group Congress (19-21 June 2011, Barcelona).

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 will increase 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 2010 research activities, which are organised into seven programmes (Genetic Medicine, Inherited Metabolic Medicine, Mitochondrial Medicine, Paediatric and Developmental Medicine, Sensorineural Pathology, Endocrine Medicine and Inherited Cancer and Related Syndromes), were compiled in

³⁴⁷ http://www.ciberer.es/documentos/Libro_Ingles.pdf

2011 Scientific Report. This report³⁴⁸ 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. CIBERER has also defined its strategy for 2012, which has been 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 translative 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 (which is attached to 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 (basic, clinical, epidemiological and translational) in the field of rare diseases.
- *Instituto de Investigación de Enfermedades Raras – IIER* (National Research Institute for Rare Diseases), within the Institute of Health Carlos III (ISCIII) was founded in November 2003 to promote basic, clinical and epidemiological research on rare diseases.
- *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. CIBERER was provided with funding amounting to €5.5 million in 2011 for research activities (basic, clinical, epidemiological and translational) in the field of rare diseases.

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 late 2009, the Sant Joan de Déu hospital and the Hospital Clínic (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 Foundation³⁴⁹, the new bank will network with other banks and institutions in Spain and other parts of Europe

ISCIII has created CAIBER (Plataforma Española de Ensayos Clínicos (Spanish Clinical Trial Platform) with the participation of 40 CRO (entities promoting research) and legal personality and attached to it as a

³⁴⁸ <http://www.ciberer.es/documentos/Memoria%20Cientifica%20CIBERER%202010.pdf>

³⁴⁹ http://www.tsf.cat/eng/quienes_somos/hservicio.php

platform for clinical trials (including rare diseases too) with a sustainable core funding of €10 million per year, that will be the Spanish leg of ECRIN (the European clinical trials infrastructure in process of constitution as an European Research Infrastructure Consortium).

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 GentxGent Foundation (Comunitat Valenciana) received €175'000 Euros from voluntary donors to fund rare diseases research projects.

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.

Participation in European research projects

Spanish teams participate, or have participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BNE, CLINIGENE, CHD-PLATFORM, CONTICANGET, CAV-4-MPS, CureFXS, EFACTS, EMSA-SG EUGINDAT, EuroRETT, ENRAH, EUGINDAT, EUMITOCOMBAT, EUROBONET, EUROAGENTEST, EUROAN LEUKEMIA NET, EUROSARC, EVI-GENORET, EUROSCA, EPINOSTICS, EUROBFNS, EuroGeBeta, GEN2PHEN, GENESKIN, HSCR, HMA-IRON, HEMO-IPS, IMMOMECE, INTREALL, LEISHMED, LEISHDRUG, LEUKOTREAT, MABSOT, MALARIA AGE EXPOSURE, MCSCS, MEFOPA, MLC-TEAM, MOLDIAG-PACA, NANOTRYP, NEUROKCNQPATHIES, NIMBL, MLC-TEAM, PNSEURONET, TRYPOBASE, RISCA, RAPSODI, RD PLATFORM, RevertantEB, SIOPEN-R-NET, SERO-TB, TAMAHUD, TREAT-NMD, and 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.

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 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)³⁵⁰.

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 (83% (57 out of 69) of the drugs with European authorisation) and for the rest, the pharmaceutical companies have not yet started commercialisation in Spain. 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 hospitals³⁵¹.

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 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 Autonomous Communities (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.

³⁵⁰ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) pp 85-86*

³⁵¹ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p 85*

Other initiatives to improve access to orphan medicinal products³⁵²

An authorisation procedure for access to non-authorised 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 satisfactory 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".

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 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.

³⁵² 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

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 diseases³⁵³, a €300,000 project, with the main objective to coordinate rare disease efforts and disseminate 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 the national focal point in the field of rare diseases.

In November 2010, the Swedish National Conference on Rare Diseases³⁵⁴ 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 Focal Point* (NFSD - *Nationella Funktionen för Sällsynta Diagnoser*) for rare diseases. 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. An inventory of available resources for people with rare diseases is one of the first tasks for the NFSD. The work will start on 1 January 2012 and the assignment has been entrusted to the non-profit rare disease care facility Ågrenska.

The Swedish Government decided in October 2011 to assign the National Board of Health and Welfare to develop a national strategy for rare diseases. The assignment will be presented in line with the Council Recommendations adapted to Swedish demands. The National Board of Health and Welfare will work together with the NFSD and other stakeholders to develop the strategy. The assignment will be presented to the Government in October 2012. The National Board of Health and Welfare is currently considering how the future work with a national strategy shall proceed.

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. Examples include four cystic fibrosis centres, one porphyria centre, one centre for children with congenital malformations and syndromes and one Rett syndrome centre. The new NFSD will collect information concerning centres of expertise in Sweden.

Pilot European Reference Networks

Swedish teams participate or have participated in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUROHISTIONET, Paediatric Hodgkin Lymphoma Network, and PAAIR.

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.

At the national level, around 70 National Quality Registries have been established³⁵⁵ and are supported by the Swedish Association of Local Authorities and Regions (SALAR). All National Quality Registries

³⁵³ <http://www.regeringen.se/sb/d/13214/a/148634>

³⁵⁴ [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)

³⁵⁵ <http://www.kvalitetsregister.se/>

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 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 Umeå³⁵⁶. 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 any 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 113 genes and estimated 158 diseases in the Orphanet database.³⁵⁷

National alliances of patient organisations and patient representation

The Swedish National Organisation for Rare Diseases (*Riksförbundet Sällsynta diagnoser = Rare diseases Sweden*) 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.

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.

³⁵⁶ <http://sfmg.se/sv/externalankar>

³⁵⁷ <http://www.orpha.net> Information extracted from the Orphanet database (September 2011).

Sources of information on rare diseases and national help lines

Orphanet activities

Since 2006 the Karolinska Institute has hosted an Orphanet team in Sweden. 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. 2011, the team also launched the Orphanet Sweden website³⁵⁸, 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.

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 almost 300 rare diseases (approximately 500 according to Orphanet categorisations). 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 100 information texts can be accessed at www.socialstyrelsen.se/en/rarediseases. The database has more than 700,000 visitors per year.

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.

NFSD is a cooperation between *Ågrenska* and the Swedish National Organisation for Rare Diseases.

Updated information on orphan medicinal products has been published by *Läkemedelsindustriföreningen* (LIF)³⁵⁹, the trade association for research-based pharmaceutical industry in Sweden.

Riksförbundet Sällsynta Diagnoser has an online database with information on sixty rare diseases.

³⁵⁸ <http://www.orphanet.se/national/SE-SV/index/hemsida/>

³⁵⁹ <http://www.lif.se/>

Good practice guidelines

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 2011 *Ågrenska* arranged twenty-two 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 2011

A number of events were organised in Sweden to mark Rare Disease Day 2011.

Swedish Orphanet team at Karolinska Institute organised a day-long seminar with the title “Rare Disease Research Forum - Challenges and Solutions” on 21 February 2011 at the Karolinska University Hospital. The purpose of the day was to gather researchers in the field of rare diseases and other stakeholders to meet and discuss rare disease research, its challenges and solutions. The day attracted around 65 attendees, the main group being clinical researchers from the Karolinska Institute. However, also representatives from Industry, the Medicinal Product Agency, the National Board of Health and Welfare, the Swedish Parliament and patient organisations participated.

Riksförbundet Sällsynta Diagnoser organised activities linked to the Rare Disease Day. In the autumn of 2011 they also launched a road show. They visited the University hospitals in Uppsala, Lund/Malmö, Gothenburg, Stockholm, Linköping and Örebro to raise awareness and to present their vision of coordinated centres for rare diseases in Sweden.

Ågrenska arranged a national conference on narcolepsy to improve holistic competence and build network. The target group was professionals with knowledge and experience of children who has developed the disease as a consequence of the Pandemrix vaccine.

Hosted rare diseases events in 2011

Amongst the rare disease events hosted and announced in *OrphaNews Europe* were:

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. A Nordic conference on rare diseases is planned to be held in 2012 and another in 2014.

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.³⁶⁰ 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.

³⁶⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp20-21).*

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 website³⁶¹ 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: ANTEPRION, BIOMALPAR, BNE, CHD PLATFORM, CUREHLH, CLINIGENE, EMVDA, EUMITOCOMBAT, EURAPS, EUCLYD, EUROSD, EUROBOONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EVI-GENORET, EMSA-SG, EUROCRAN, EURADRENAL, EURAMY, EURO-GENE-SCAN, GENESKIN, HDLMOICS, INHERITANCE, NMD-CHIP, LYMPHANGIOGENOMICS, MANASP, MOLDIAG-PACA, NEUPROCF, NEOTIM NEUROPRION, NEWTBDRUGS, PRIBOMAL, PWS, TRYPOBASE, TB-DRUG OLIGOCOLOR, TREAT-NMD, RD PLATFORM and VITAL.

E-Rare

Sweden is not currently a partner of the E-Rare project.

IRDiRC

Swedish funding agencies are not currently committed members of 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)³⁶² 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

³⁶¹ www.mun-h-center.se

³⁶² www.mpa.se

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 68 orphan medical products (OMPs) that were authorised by December 2011, 51 OMPs were sold in Sweden during 2011. These products are Afinitor*, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme**, Firazyr, Glivec**, Gliolan, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Replagal**, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tasigna, Thalodimide Celgene, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votuvia, Vpriv, Wilzin, Xagrid, Yondelis and Zavesca³⁶³.

The Dental and Pharmaceutical Befefits Board (DPBB) has decided to reimburse 32 of these OMPs, some with restrictions. The reimbursement system does not include medicinal products used in hospitals. When a drug is not subsidised, the individual counties/regions decide whether a patient should get access to a treatment. This means that the availability of OMPs may vary in different parts of the country.³⁶⁴

Orphan medicinal product pricing policy

The DPBB decides 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 councils³⁶⁵.

Orphan medicinal product reimbursement policy

Reimbursement decisions are made by the DPBB³⁶⁶, 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 DPBB, OMPs are fully reimbursed by social 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. Solidarity funding between Swedish county councils is available for three diseases, two of which are rare diseases (Gaucher's disease and haemophilias): the basis for the solidarity funding of these very rare diseases is to compensate for costs due to the uneven distribution of these patients between the different areas in Sweden. Concerning drugs used in hospitals (orphan or non-orphan), the decision on availability for the patients as well as the payment is decided at the local hospital/county level since in-hospital drug costs are not included in the reimbursement system.

In total, 32 OMPs are on the reimbursement list as of May 2011: Afinitor, Aldurazyme, Cabaglu, Ceplene, Cystadane, Diacomit, Duodopa, Exjade, Fabrazyme, Firazyr, Glivec, Increlex, Inovelon, Lysodren, Nexavar, Nplate, Orfadin, Prialt, Replagal, Revatio, Revlimid, Revolade, Somavert, Sprycel, Tasigna, Thalidomide Celgene, Tracleer, Ventavis, Volibris, Wilzin, Xagrid and Zavesca. Duopdopa, Revlimid and Volibris were listed subject to certain conditions and DDPB decided on a reimbursement on a case-by-case basis for Nexavar in hepatocellular carcinoma. Several other drugs are marketed in Sweden without general reimbursement³⁶⁷.

Other initiatives to improve access to orphan medicinal products

Compassionate use of OMPs is being introduced in Sweden and in the future will be 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.

Orphan devices

No specific information reported.

³⁶³ *The product has been withdrawn by the sponsor from the Registry of Orphan Medicinal Products; **The product has been removed from the Registry of Orphan Medicinal Products since its 10 years of market exclusivity has expired. For Glivec this applies to the acute lymphatic leukaemia indication only.

³⁶⁴ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 59-62)

³⁶⁵ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011) p117

³⁶⁶ www.tlv.se

³⁶⁷ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues*, Donald Macarthur (2011) p118

Specialised social services

Ågrenska offers families, adults and children the possibility to benefit from programmes that provide guidance to patients regarding 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.³⁶⁸

There have been no new initiatives in 2011 in this area.

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

The basic concept in the National Health Service is not that of 'rare diseases' but rather that of 'specialised services'. There are three tiers for the planning and management of health services – local, specialist commissioning and national commissioning. 'Specialist commissioning' applies to any service with a planning population of 1 million or more, such as rare diseases. Services are selected into national commissioning by ministerial decision³⁶⁹. This involves an assessment of the population's needs and deciding what to prioritise taking into account a wide range of factors. A comprehensive list of services likely to need specialist commissioning has been developed (the Specialised Services National Definition Set).

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 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.

In 2010 it was announced that a new advisory body will be created in England covering specialised services and treatments for extremely rare conditions typically affecting fewer than 500 patients. Following a consultation, the current National Commissioning Group was dissolved and a new body, the Advisory Group on National Specialised Services (AGNSS), was established. AGNSS makes recommendations directly to Ministers about which services should be designated for national commissioning. The Group will also consider a small number of new technologies for small patient populations which fall outside the National Institute for Health

³⁶⁸ <http://www.vgregion.se/upload/HoH/Kansli/R%c3%a5d%20och%20st%c3%b6d/lss-engelska-hso-hoh.pdf>

³⁶⁹ List and criteria are available at www.ncg.nhs.uk

and Clinical Excellence's (NICE) remit, but which may be suitable for national specialised commissioning. Any decisions that AGNSS will make about services and technologies will be guided by a decision-making framework which draws in part on work done by the Specialised Healthcare Alliance³⁷⁰ around ethical considerations. Membership of the group is wide-ranging and includes both commissioning and clinical representation, as well as an ethicist³⁷¹. AGNSS met for the first time in September 2010.

Services for certain very rare conditions (generally less than 400 people nationally) were previously commissioned by the NCG, a standing committee of the NSCG. A list of specialised services³⁷² (see section on "National plan for rare diseases and related services") is available for use in determining whether services should be commissioned locally or by the specialist commissioning group, but there is no official list of rare diseases: this applies to England. Different but equivalent arrangements exist in Scotland, Wales and Northern Ireland. Health ministers in England agreed to national commissioning of services, effective 1 April 2011, for 6 more rare diseases: Stickler syndrome; Wolfram syndrome; Lymphangiomyomatosis; Insulin resistance syndromes (e.g. Donohue and Rabson Mendenhall syndromes); Severe and complex forms of osteogenesis imperfecta; and Pseudo-obstruction of gut in young children.

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

Although there are these measures in place, a national plan or strategy for rare diseases in the UK has not yet been adopted in the UK. The plan should be produced by the end of 2013.

Rare Disease UK (RDUK) has campaigned for the adoption of a plan for rare diseases and met with government officials and key people within the National Health Services in all four home nations to highlight the need for a strategy for rare diseases. RDUK also established 5 working groups comprising of expert stakeholders looking into various aspects of planning for rare diseases in the UK in order to aid the establishment of a plan. A UK National Conference on Rare Diseases, organised by RDUK and EURORDIS in the context of the Europlan conference, took place on 16 November 2010³⁷³ in Manchester to examine proposals for a plan which were then launched on Rare Disease Day 2011. The proposals took the form of a report entitled 'Improving Lives, Optimising Resources: A Vision for the UK Rare Disease Strategy'³⁷⁴, presented at the House of Commons on 28 February 2011. The report outlines 27 broad recommendations from RDUK and over 85 specific recommendations covering five areas which an effective strategy needs to address: the coordination of research, prevention and diagnosis, commissioning and planning, patient care, information and support, and delivering coordinated care. All four health departments across the UK have signalled their willingness to take on board RDUK's recommendations in developing a strategy for rare diseases and to work in collaboration with the group.

The Specialised Healthcare Alliance (SHCA) held on 16 November 2010 the SHCA Conference on Delivering Quality in Specialised Care. The conference was opened by the Minister for Quality at the Department of Health. This conference helped inform the 2011 report "*Leaving No One Behind: Delivering High Quality, Efficient Care for People with Rare and Complex Conditions*"³⁷⁵ (see section on "National patient alliances of patient organisations and patient representation"): this report was part of the iterative process

³⁷⁰ <http://www.shca.info/index.htm>

³⁷¹ A full list of participants is provided here: <http://www.specialisedservices.nhs.uk/info/agnss>

³⁷² List and criteria of specialised services, developed by the Department of Health and now held by the National Specialised Services Team, are available at www.ncg.nhs.uk

³⁷³ [http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report uk europlan.pdf](http://download.EURORDIS.org/europlan/2%20EUROPLAN%20Guidance%20Documents%20for%20the%20National%20Conference/final%20report%20uk%20europlan.pdf)

³⁷⁴ www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf

³⁷⁵ <http://www.shca.info/PDF%20files/SHCA%20Report%202011%20low%20res.pdf>

seeking to inform the UK's response to the EC Council Recommendation on an action in the field of rare diseases, as well as future arrangements for specialised commissioning.

A national plan, aided by the recommendations made by these groups, was developed during 2011. The public consultation was launched on 29 February 2012 to mark Rare Disease Day 2012³⁷⁶. The UK-wide consultation will be open until 25 May 2012. Responses to the consultation will inform the final plan, due to be produced by the end of 2013. The proposed plan recommends using specialist centres to make exact diagnosis; acknowledges that all doctors should have the right training to be aware of the possibility of a rare disease; and recommends that the care of patients with rare diseases be better coordinated.

Other related actions

The British Paediatric Surveillance Unit (BPSU) was established in 1986 to allow paediatricians to contribute to the epidemiological surveillance and further study of rare disorders affecting children. The BPSU publishes an each year a Scientific Annual Report³⁷⁷. This study typically includes 12 rare childhood disorders (or rare complications of common diseases) "of such low incidence or prevalence as to require cases to be ascertained nationally in order to generate sufficient numbers for study". Surveillance of conversion disorder has involved the newly established UK Child and Adolescent Surveillance System which investigates rare child psychiatric conditions. The report also includes a progress report of the international network of paediatric surveillance units (INoPSU). Following the establishment of the BPSU, other countries have developed similar methodologies, including Australia, Germany, Greece, Latvia, the Netherlands, New Zealand, Portugal, and Switzerland. Scotland and Belgium, though not yet members of the network, have similar such units, there is also interest in Argentina and Italy. International-level action over the past two years, according the report, includes the surveillance of 70 different rare conditions covering a child population of over 50 million and involving over 10,000 clinicians. Regular conferences are held the most recent being in 2010 in Dublin Ireland. A report of the conference and INoPSU activities are available from their annual report³⁷⁸.

Deciphering Developmental Disorders (DDD)³⁷⁹ was launched in 2011: this project aims to improve the diagnosis and care of children in the UK who fail to develop normally due to changes in their genetic makeup. The project seeks to capture the genetic make-up of up to 12 000 children with intellectual or physical delays or who have multiple malformations. A collaborative effort between the National Health Service Clinical Genetics Services across the UK and the Wellcome Trust Sanger Institute, the project will provide information for researchers and clinicians into rare chromosomal abnormalities and their possible role in disease. Another interesting facet to be explored by the project are the ethical and social aspects involved in the clinical use of new genomic technologies, including the perceptions and expectations of patients and families. The project is supported by the Health Innovation Challenge Fund, a parallel funding partnership between the Wellcome Trust and the Department of Health.

In 2011, the United Kingdom's first brain tumour tissue bank was created, housed in Southern General Hospital in Glasgow, Scotland. It will provide a large number of samples to researchers, with the goal of accelerating research toward treating this group of rare diseases. The new tissue bank, available to researchers from academia and industry, was made possible by funding from brain cancer charity Brainstrust³⁸⁰.

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.

Health ministers in England have agreed to national commissioning of services, effective 1 April 2011, for patients with the following disorders: Stickler syndrome; Wolfram syndrome; Lymphangiomyomatosis; Insulin resistance syndromes (e.g. Donohue and Rabson Mendenhall syndromes); Severe and complex forms of osteogenesis imperfecta; and Pseudo-obstruction of gut in young children. National commissioning establishes

³⁷⁶ <http://www.dh.gov.uk/health/2012/02/consultation-rare-diseases/>

³⁷⁷ <http://www.rcpch.ac.uk/what-we-do/bpsu/publications/annual-reports/annual-reports>

³⁷⁸ <http://www.inopsu.com/publications/INoPSUAnnualReport2009.pdf>

³⁷⁹ <http://www.sanger.ac.uk/about/press/2011/110322.html>

³⁸⁰ http://www.gla.ac.uk/news/headline_212335_en.html

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.

Pilot European Reference Networks

British teams participate or have participated in the following European Reference Networks for rare diseases: Dyscerne (main partner), ECORN CF, EPI/EPNET, ENERCA, EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma network, PAAIR, Care-NMD and EN-RBD.

Registries

In the UK registers are kept for individual conditions and some groups of conditions, including congenital anomalies.

The United Kingdom contributes to the following European registries: EUROCAT, EIMD, TREAT-NMD, AIR, EURO CARE-CF, EURO-WABB, EUHASS, EUROPAC, European Prader-Willi database and EUROWILSON.

Neonatal screening policy³⁸¹

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>.

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 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 devolved country; England, Northern Ireland, Scotland and Wales. 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.

³⁸¹ <http://www.screening.nhs.uk/programmes>

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.ukgt.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. A small project team and three working groups carry out the work on behalf of the Clinical & Scientific Advisory Group and 53 member laboratories from regional genetics and specialist laboratories.

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 current arrangements for the Specialised Commissioning Groups in each region and recently published a report 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”. During the debate in the House of Lords in June 2010, on the report from the inquiry, the Parliamentary Under-Secretary of State, Earl Howe, endorsed the work that UKGTN is undertaking with commissioners of genetic services. The Department of Health continues to support this work to develop a consistent model and guiding principles which will also inform commissioning of genetic testing in mainstream specialties.

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 have been funded by the Department of Health since 2002 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 GEN2PHEN³⁸² 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 Tests 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

³⁸² www.gen2phen.org

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 2011 the UKGTN had evaluated 313 gene dossiers and made recommendation for 243 tests to be available for NHS service. During this time 255 testing criteria were developed. There are less testing criteria because this was concept was not introduced until 2006. 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.

Tests for patients in the NHS are funded through NHS commissioning mechanisms.

It has been recognised that activity data collection from laboratories across the country is variable due to different methods of recording activity and therefore funding in each area is not comparable. The UKGTN has worked in collaboration with the Clinical Molecular Genetics Society (CMGS) to develop a reliable and easy to use workload measure for molecular genetic testing to be able to compare activity data across labs. The unit of activity developed is based on patient reports and is known as Molecular Units (MoUs). Each report is categorised into one of seven bands according to its complexity which is measured according to how many PCR amplicons or equivalent are involved in the test. Each band has a weight assigned to it and the number of reports in that band is multiplied by the weight to arrive at the number of MoUs of activity for a laboratory. The weights range from 1 for a DNA extraction report i.e. no testing within the lab to a weight of 40 for a band G report which involves testing and analysing over 100 amplicons. The weightings were established following testing by 6 pilot UKGTN laboratories of various sizes and with varied testing repertoires. Laboratory reports and the number of amplicons are relatively easy to count and allow for a transparent and flexible system that could also be used to allocate national tariffs. Laboratories are currently trialling this system for workload in 2010/2011. The Clinical Molecular Genetics Society and the UKGTN are collaborating with the Association for Clinical Cytogenetics to develop a similar system for cytogenetic testing. The CMGS issued an annual audit³⁸³ of in 2011 genetic testing activity. 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. The 2009-2010 audit "...shows a continued growth in national activity for each of the postnatal, prenatal and predictive testing categories, an improvement in routine reporting times and encouraging data of the capturing and utility of activity...". Prenatal diagnosis reports were recorded for 120 different disorders, with 86% being for common aneuploidies. There were 12839 prenatal reports, of which 1744 were for disorders excluding aneuploidy. Non-invasive foetal sexing testing accounted for 19% of non-aneuploidy screening. Monogenic disorders include sickle cell anaemia (440), beta-thalassaemia (119), SMA type I (61), Duchenne muscular dystrophy (32), Huntington disease (25), craniosynostosis (9), and others. For postnatal activity, there was a 31% increase in single gene disorders for 2009-2010. This jump reflects the inclusion of data from a new large volume provider. There was a mean number of 789 reports for fragile X testing across 18 providers. There was a mean number of 706 cystic fibrosis reports across 20 providers.

In 2009 the National Genetics Reference Laboratories in the UK launched an innovative free online diagnostic technology forum destined for professionals in the field of genetic testing. Professionals internationally can share in-house assessments of diagnostic technologies ranging from diagnostic kits and sequencing platforms to analysis software. LabSight is a non-profit tool in response to a lack of reliable comparative reporting on new technologies. The forum will serve as an online resource for documentation, and will also list upcoming events and calls for collaborations. With rare disease research and diagnostics particularly vulnerable to limited budgets and resources, LabSight offers a money-saving tool helping professionals find the best technology for their diagnostic laboratories.

A new report³⁸⁴ from the Foundation for Genomics and Population Health (commonly known as the PHG Foundation) encourages the mainstream medical specialities to become versed in the field of genetics, incorporating genetic knowledge and technology into their offer. The authors of the report propose "...a shift of the axis of main clinical responsibility for individual patients with inherited disease from clinical genetics to the relevant specialty - cardiology, ophthalmology, renal medicine, neurology or a host of other areas". Evoking a future in which, "...rather than genetics 'moving into mainstream medicine' ... clinical areas develop and

³⁸³ http://www.cmgs.org/CMGS%20audit/2010%20audit/secure4Final_Audit09_10.pdf

³⁸⁴ <http://www.phgfoundation.org/file/7962/>

expand to integrate new clinical expertise relevant to inherited disease and a new set of genomic technologies into clinical pathways as relatively specialised areas within their own service", the report acknowledges that close cooperation with specialist clinical and laboratory genetics service would be necessary in order to promote and sustain such a shift.

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 2011-2012³⁸⁵ 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 541 genes and an estimated 585 diseases in the Orphanet database³⁸⁶. The UKGTN has recommended tests for 536 diseases and 714 genes for NHS commissioning for service from April 2011.

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 UK³⁸⁷ (formerly the Genetic Interest Group). 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 UK³⁸⁸ (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 document³⁸⁹ 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.

RDUK launched a new report entitled 'Improving Lives, Optimising Resources: A Vision for the UK Rare Disease Strategy'³⁹⁰ at the House of Commons on 28 February 2011. The report outlines 27 broad recommendations from RDUK and over 85 specific recommendations covering five areas which an effective strategy needs to address: the coordination of research, prevention and diagnosis, commissioning and planning, patient care, information and support, and delivering coordinated care. All four health departments across the UK have signalled their willingness to take on board RDUK's recommendations in developing a strategy for rare diseases and to work in collaboration with the group. Following consultation and production of the strategy, RDUK will then be scrutinising the implementation of a strategy.

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 overview³⁹¹ and critique of England's new arrangements for health service

³⁸⁵ <http://www.nowgen.org.uk/CubeCore/uploads/documents/NowgenReviewandWorkProgramme20112012.pdf>

³⁸⁶ Information extracted from the Orphanet database (September 2011).

³⁸⁷ <http://www.geneticalliance.org.uk/>

³⁸⁸ <http://www.raredisease.org.uk/>

³⁸⁹ http://www.raredisease.org.uk/raredisease_strategy_consultation.htm

³⁹⁰ www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf

³⁹¹ <http://www.shca.info/PDF%20files/The%20challenge%20of%20rarity%20-%20FINAL.pdf>

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 is consulting about a number of aspects of how the NHS in England will work, including the future of the proposed Innovation Pass that would allow funding of orphan products for a period of up to three years pending their appraisal.

In 2011 the SHCA published a new report. *“Leaving No One Behind: Delivering High Quality, Efficient Care for People with Rare and Complex Conditions”*³⁹² 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*³⁹³. 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.

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 UK³⁹⁴ - as well as the updated slogan and logo more accurately reflect the work of the group.

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.

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.

Sources of information on rare diseases and national help lines

Orphanet activity in the United Kingdom

Since 2004 there is a dedicated Orphanet team in the United Kingdom, hosted by the University of Manchester. Orphanet UK is in charge of collecting and validating data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in the United Kingdom and in Ireland for entry into the Orphanet database. The Orphanet UK team maintains the Orphanet UK national website³⁹⁵. This team was officially designated by the Department of Health as the official Orphanet team in the United Kingdom in 2010.

³⁹² <http://www.shca.info/PDF%20files/SHCA%20Report%202011%20low%20res.pdf>

³⁹³ <http://www.shca.info/PDF%20files/Registries%20Guide%20-%20FINAL.pdf>

³⁹⁴ <http://www.geneticalliance.org.uk/index.html>

³⁹⁵ <http://www.orphanet.co.uk>

Orphanet UK is represented at many major conferences and events such as workshops on rare diseases and the Rare Disease Day. 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 Dysmorphology), 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 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 Unique³⁹⁶ 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

Nowgen³⁹⁷, a centre of excellence in public engagement, education and professional training in biomedicine, part of the NIHR Manchester Biomedical Research Centre, in collaboration with Dyscerne³⁹⁸ 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 methodologies³⁹⁹.

A range of other guidelines for rare and very rare diseases are posted on the NCG website⁴⁰⁰ or published in professional journals.

New guidance document⁴⁰¹ 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

³⁹⁶ <http://www.rarechromo.org/html/home.asp> and <http://www.rarechromo.org/html/LeafletProtocol.asp>

³⁹⁷ www.nowgen.org.uk

³⁹⁸ www.dyscerne.org

³⁹⁹ www.dyscerne.org/dysc/Guidelines & <http://www.mangen.co.uk/professionals/clinical-services/useful-documents.aspx>.

⁴⁰⁰ www.ncg.nhs.uk

⁴⁰¹ <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

A training session entitled 'Update in Neuromuscular Disorders' was held for the fourth year at the National Hospital for Neurology and Neurosurgery (13-16 June 2011). 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 2011

The UK based charity 'Jeans for Genes' holds an annual awareness day to raise funds for genetic disorders⁴⁰².

To mark Rare Disease Day 2011, RDUK coordinated a number of events across the UK. RDUK also launched a new report entitled 'Improving Lives, Optimising Resources: A Vision for the UK Rare Disease Strategy'⁴⁰³ at the House of Commons on 28 February 2011, which was presented to Earl Howe, Minister at the Department of Health. The event brought together patient organisations, patients, carers, healthcare providers, clinicians, researchers, health workers, industry representatives and policy makers. Over one hundred and fifty delegates attended, representing more than one hundred organisations. The report outlines RDUK's recommendations for a strategy for rare diseases and is a product of a year and a half of work in collaboration with members and the broad rare disease community. Receptions were also organised at the Scottish Parliament (22 February 2011) Northern Ireland and Welsh Assemblies (16 March 2011) by RDUK and Genetic Alliance UK. At each of the events, attendees who participated in RDUK's contact campaign took the opportunity to meet with their local politician. Many other patient organisations mark the day with events.

Other events included the Annual Conference of Genetic Alliance UK (24 May 2011), 6th British Society Human Genetic (BSHG) Conference (5-7 September 2011).

Hosted rare disease events in 2011

Amongst the rare disease related events hosted by the UK and announced in *OrphaNews Europe* were: International Tuberous Sclerosis Complex Research Conference 2011 (21-24 September 2011, Belfast), Expanding Horizons in Friedreich Ataxia (6 October 2011, London), and the 5th International Workshop on AKU (Alkaptonuria) (18-19 November 2011, Liverpool).

Research activities and E-Rare partnership

National research activities

Rare diseases research has been supported in the UK up till now although no special funding mechanism is as of yet in place. Government funding is mostly available through the Research Councils (i.e. the Medical Research Council) and the National Institute for Health Research (NIHR). 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).

The Biomedical Research Centres, funded by the National Institute for Health Research (NIHR), also fund some research on rare diseases. The Manchester Biomedical Research Centre specialises in genetics and developmental medicine and is a leader in engaging and involving patients/publics in the research process. The patient involvement and public engagement programme for Manchester Biomedical Research Centre is led by Nowgen. Nowgen has undertaken a detailed mapping exercise with researchers and identified excellent practice. A comprehensive strategy for engagement and involvement has been developed by Nowgen and is being implemented through training courses and resources to support researchers. Examples of Nowgen's current work include: investigating young peoples' information needs when taking part in clinical research and developing a DVD in partnership with teenagers about gene therapy for Cystic Fibrosis. The London-based Biomedical Research Centre in London of the National Institute for Health Research (NIHR) has developed in 2010 a guide intended to aid researchers to involve patients, carers, families and patient groups in the various

⁴⁰² <http://www.jeansforgenes.com/about>

⁴⁰³ www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf

stages of research⁴⁰⁴. These include the development of grant applications, the design/management of research, the undertaking of research, the analysis of the research data, and the dissemination of research findings. The guide outlines ways in which patients and other users can be involved in each of these stages and how researchers can facilitate this involvement. In a press release, Dr David King, Director, NIHR Central Commissioning Facility is quoted as saying that “*Patient and Public Involvement (PPI) will increase in importance in the work of all NIHR Biomedical Research Centres and Units as it is increasingly recognised that PPI is a win/win for both patients and researchers. This new guide for research staff will greatly enhance PPI across the NIHR, especially in the area of experimental medicine.*” Experimental medicine is an important area in the field of rare diseases.

Participation in European research projects

British teams participate or have participated in European rare disease research projects including: AAVEYE, ANTEPRION, ANTIMAL, BIG HEART, BIOMALPAR, BNE, CARDIOGENET, CHD PLATFORM, CHEARTED, CRUMBS IN SIGHT, CILMALVAC, CLINIGENE, CONTICANET, CSI-LTB, EMSA-SG, EUROCRAN, EMVDA, EURADRENAL, ENRAH, EPOKS, EUMITOCOMBAT, EURAMY, EUREGENE, EURO BONET, EURO CARE CF, EURO GENTEST, EURO GLYCANET, EURO IRON1, EURO SCA, EURO TRAPS, EUCILIA, EURO-LAMINOPATHIES, EUNEFRON, EURO PADNET, EUROWILSON, ENCE-PLAN, EVI-GENORET, ESDN, GEN2PHEN, GENESKIN, INHERITANCE, HUMALMAB, LEISHDNAVAX, PWS, MITOTARGET, MPCM, MALARIA AGE EXPOSURE, MITOCIRCLE, MM-TB, MOLDIAG-PACA, MPCM, MYELINET, MYORES, NEOTIM, NEUPROCF, NEUROKCNQPATHIES, NEUROPRION, NEUROSIS, PSYCHCNVS, NEWTBDRUGS, PNSEURONET, PULMOTNESION, PWS, RATSTREAM, SPASTICMODELS, RD PLATFORM, STEM-HD, TAMAHUD, 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 currently a committed member of the IRDiRC.

Orphan medicinal products⁴⁰⁵

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) has 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 basis⁴⁰⁶.

Orphan medicinal product incentives

No specific incentives reported.

Orphan medicinal product market availability situation

No specific information has been provided concerning orphan medicinal products launched on the market in the United Kingdom.

⁴⁰⁴ <http://www.guysandstthomas.nhs.uk/news/newsarchive/newsarticles/20100512user-involvement-guide.aspx>

⁴⁰⁵ Written using information from *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp 62-66)

⁴⁰⁶ *EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, C. Hahl, F. Bachner (2011) p61

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 medicines⁴⁰⁷.

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 funds certain orphan medicinal products at national level.

Other initiatives to improve access to orphan medicinal products^{408,409}

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) will start commissioning expert assessments for off-label medicine use starting spring 2012⁴¹⁰. These assessments will not constitute formal guidance, but rather will 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.

Orphan devices

No specific information reported.

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.

⁴⁰⁷ *Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Access Issues*, Donald Macarthur (2011) pp.86-7

⁴⁰⁸ Written using information from *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp 62-66)

⁴⁰⁹ 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).

⁴¹⁰ <http://www.nice.org.uk/newsroom/news/BetterInformationOnUnlicensedDrugS.jsp>

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 Diseases⁴¹¹ 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 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 First National Conference on Rare Diseases (17-19 September 2010)⁴¹², 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 (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

⁴¹¹ <http://www.rijetke-bolesti.org>

⁴¹² http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Croatia_n_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

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.

Pilot European Reference Networks

Croatian teams participate, or have participated, in the following European Reference Networks for rare diseases: TAG and TREAT NMD and Care-NMD.

Registries

Currently, there is neither a national registry for rare diseases in Croatia, nor a national committee dedicated to registries for rare disorders. However, many patients are registered through the mentioned referral centres and patient organisations (phenylketonuria, 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 is 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 37 diseases in the Orphanet database⁴¹³. 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 Diseases⁴¹⁴ has been working on developing relations with the stakeholders who have an impact on the lives of rare diseases patients. The Society is a coalition of patient groups and NGOs. The Society cooperates with the Ministry of Health and Social Welfare, the Croatian Institute for Health Insurance and other national health institutions, national and European-level civil society organisations, and medical professionals who work with rare disease patients. In 2011 the Society elected a new president, and was supported by an employee. The Society works to raise general awareness concerning rare diseases and lobbies political stakeholders. Thanks to the initiatives of the CSPRD, the Croatian President declared 2008 the Year of Rare Diseases and offered assistance for future actions.

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.

⁴¹³ Information extracted from the Orphanet database in September 2011.

⁴¹⁴ <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.

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 center, 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

There is currently no national rare disease help line in Croatia. Informal help lines run by patient organisations provide general information for rare diseases diagnostic and management. The national alliance has started the preparations for the official help line. It should be available in 2012 after the education of volunteers and a media campaign. It will be financed through the project and by donations.

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 2011

In Croatia, there are regular professional meetings dedicated to rare diseases organised by the Croatian Society for Human Genetics, Croatian Society for Rare Diseases, the Section for Metabolic Diseases of the Croatian Paediatric Society and different professional and patient organisations.

A Rare Disease Day press conference was organised in Zagreb on 23 February 2011, by the Croatian Society for Rare Diseases. The main goal was to emphasise the issues we are dealing with, such as this year's topic - inequality. The press conference was held at the City Zagreb's Forum Venue and was supported by the City Zagreb's Department of Health. Rare Disease Day was once again supported by President Prof. dr. Ivo Josipović, who gave a video message to be conveyed to the public by TV in order to raise the public and media awareness about rare diseases.

In addition to this event, Croatia's four biggest cities (Zagreb, Split, Rijeka and Osijek) marked the Rare Disease Day with a range of activities. Information booths were placed in the square in four major cities informing the public about rare diseases. Public lectures were given in order to bring more clarity to the issue of rare diseases and to share experiences of those affected by rare diseases. A round table meeting took place with the participation of medical professionals, health administration representatives and rare diseases patient in Zagreb on 28 February 2011.

During the Fifth Croatian Congress on Human Genetics from 20 to 24 June 2012, there was a round table discussion dedicated to rare diseases, with participation of the experts and representatives of patients groups.

Hosted rare disease events in 2011

Rare disease related events hosted by Croatia included the 2nd Assembly of the European Myasthenia Gravis Association (EuMGA) in (26 February 2011, Zagreb), Ninth European Paediatric Neurology Society Congress (11-14 May 2011, Cavtat) and the Annual General Meeting of the Osteogenesis Imperfecta Federation Europe in (2-5 October 2011, Dubrovnik).

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.

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 are not yet committed members of 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 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 recently been solved. The latest list of orphan medicinal products approved for treatment of rare and severe diseases (Decision, Narodne novine, 131/10, 24 November 2010) can be found on the web pages of the Croatian Agency for Drugs and Medicinal Products⁴¹⁵. 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.

⁴¹⁵ www.halmed.hr

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 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 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.

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 2011, there were no new initiatives in the field of respite care: some individual patient organisations and some groups of patients organised summer camps (e.g. PKU, haemophilia).

2.2. 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.

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.

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 preventive population genetic screening. Four of these screening tests are provided for free. Many of the tests are reimbursed (specific mutation testing or linkage, prenatal chromosomal microarray), but sequencing of genes and postnatal chromosomal microarray are not reimbursed and patients pay for these tests privately. Genetic testing in the private labs in Israel and abroad is possible, but it is not reimbursed and patients pay for these tests privately. In the Orphanet database, 227 genes are tested in Israel for 237 diseases⁴¹⁶. 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 website⁴¹⁷ in Hebrew.

Official information centre for rare diseases

No specific information reported.

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 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.

⁴¹⁶ Information extracted from the Orphanet database (September 2011).

⁴¹⁷ <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/>

National rare disease events in 2011

For the first time, to mark Rare Disease Day 2011, a one day conference was organised by Orphanet Israel at the Schneider Children's Medical Center of Israel on 28 February 2011. There were about 300 participants including parliament and Ministry of Health representatives, physicians and patients.

Hosted rare disease events in 2011

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: EMSA-SG, SIOPEN-R-NET, ANTEPRION, AUTOROME, CLINIGENE, EUGINDAT, EUROCARE CF, EUROGLYCANET, EURO-IRON1, EUROPEAN LEUKEMIA NET, GENOMIT, LEISHMED, MYASTAID, MYORES, NEUROPRION, PWS, STEM-HD, EUROTRAPS, FIGHT-MG, LEISHDRUG, MYELINET, NEURO.GSK3, NEUROSIS, NGIDD, ELA2-CN, EUROGEBETA, RHORCOD, RARE-G, TRANSPOSMART, 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.

IRDiRC

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

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.

Orphan devices

A draft law on this subject has been proposed.

Specialised social services

No specific information reported.

2.3. 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 have been an area of priority in the government's 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 report⁴¹⁸ on 1 December 2010. The recommendations were supported by the Directorate, with some following remarks. In March 2012 the Ministry announced that the South-Eastern Norway Regional Health Authority (RHF) shall 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 the Ministry will conclude later). The RHF will receive resources to establish this unit in 2013.

In addition to this the Regulation on "Approval of hospitals and national services", 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 published⁴¹⁹.

⁴¹⁸ http://www.helsedirektoratet.no/vp/multimedia/archive/00316/Revidert_rapport_Sa_316599a.pdf

⁴¹⁹ Unofficial translation: <http://www.regjeringen.no/upload/HOD/SHA/forskrift-eng-270911.pdf>

Centres of expertise

National competence service

In Norway there are 16 different state-financed centres of expertise for people with rare and less known disorders. 12 of the centres are national competence services, providing services for more than 16'000 persons with more than 300 different rare disorders which lead to disability. In order for a service to be established for a rare disease, the condition must furthermore meet the criteria of being "congenital and complex/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 Regional Health Authorities as specialist health care services. The grants to the centres are ear marked to the RHAs 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.

The Norwegian Directorate for Health has also received the results of a commissioned survey⁴²⁰ carried out by marketing research firm Ipsos MMI (previously Synovate) that sought to explore the knowledge of 11 of the national centres of expertise for rare disorders in Norway. The survey shows an over-all demand for a centralised telephone/postal resource for the centres of expertise, and a global lack of knowledge of where to obtain information on rare disorders. The Norwegian Directorate of Health is the country's competent authority, responsible for technical as well as certain administrative duties. The Rehabilitation and Rare Disorders Department at the Directorate maintains a free help-line for rare conditions available to patients, family members and service providers. The results from the survey show that this service should be better marketed.

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.

Pilot European Reference Networks

Norwegian teams participate/participated, in the following European Reference Networks for rare diseases: Dyscerne, Paediatric Hodgkin Lymphoma Network, EPNET and Care-NMD.

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, EUROCARE, EPR (European Porphyria Registry) and EUROCAT 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 January 1, 2012. Under this regulation, prior to newborn screening, it is expected that the parents are well informed about tests, methods and possible consequences. Newborn screening will 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

⁴²⁰ http://www.helsedirektoratet.no/funksjonshemminger/etterlyser_felles_sentral_for_sjeldensentrene_685144

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.genetikportalen.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 110 genes and an estimated 117 diseases in the Orphanet database⁴²¹.

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 Directorate will follow up this report.

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 Norway⁴²² 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 services⁴²³. 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 800 different rare disorders.

Other sources of information

The Directorate's website also 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 source of information is the Directorate's website⁴²⁴.

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 diseases (e.g. <http://www.sjeldnediagnoser.no/?k=sjeldnediagnoser/home&aid=10960>).

⁴²¹ Information extracted from the Orphanet database (September 2011).

⁴²² <http://www.orpha.net/national/NO-NO/index/kort-om-orphanet/>

⁴²³ Accessible on these sites amongst others <http://www.sjeldnediagnoser.no/> and <http://www.frambu.no/>

⁴²⁴ <http://www.helsedirektoratet.no/helse-og-omsorgstjenester/sjeldne-tilstander/Sider/default.aspx>

National rare disease events in 2011

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.

Frambu Resource Centre for Rare Disorders marked the Rare Disease Day 2011 by organizing an interview with two families having a child with a rare disease. The interview was broadcasted by the Norwegian Broadcasting Association in their evening news. The interview was located at Frambu and we also got the possibility to inform about the struggle for people diagnosed with a rare disease. Another interview with a third family was made by the Norwegian News Agency (NTB) who published the story in different newspapers all over Norway.

Hosted rare disease events in 2011

No other rare disease events were hosted by Norway in 2011.

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: CHEARTED, ECFR, EUROCRAN, EURAPS, EURADRENAL, EURO BONET, HUE-MAN, MYELINET, NEUROXSYS, NEUROKCNQPATHIES, SIOPEN-R-NET and VITAL.

E-Rare partnership

Norway is not currently a partner of the E-Rare project.

IRDiRC

Norwegian funding agencies are not yet committed members of 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 2011, 48 orphan medicinal products were marketed in Norway. These drugs are: Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Duodopa, Elaprase, Esbriet, Evoltra, Exjade, Firazyf, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Revatio, Revlimid, Savene, Soliris, Somavert, Sprycel, Tassigna, Tepadina, Thalodimide Celgene, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Wilzin, Xagrid, 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.

An open-access article⁴²⁵ appearing in the *British Medical Journal* depicts the attitudes in Norway towards orphan medicinal product funding, finding that “*despite strong general support for statements expressing a desire for equal treatment rights for patients with rare diseases, there was little evidence that a societal preference for rarity exists if treatment of patients with rare diseases is at the expense of treatment of those with common diseases*”. The authors, working from the premises that “*drugs for rare diseases (orphan drugs) seldom meet standard cost effectiveness thresholds used to evaluate new drugs [and that] some studies suggest that only a societal preference for rarity would justify granting exceptions to cost effectiveness thresholds for orphan drugs*”, sought to determine whether a preference for rarity justified ignoring considerations of cost-effectiveness. Using a cross-sectional web-based survey, over 1500 Norwegians between the ages of 40 and 57 were queried on their opinions toward funding for rare versus common diseases and the allocation of funds when rare disease treatments were costlier. The authors conclude that there exists, “*...little compelling evidence ... to support the existence of a societal preference for rarity in itself, a finding that supports the view that treatments for rare disease should not be exempt from standard considerations of cost effectiveness.*” However, the authors point out that there could be “*unexplored ethical reasons*” that would support a special funding status for orphan medicinal products. Furthermore, the authors concede that “*...majority opinion is not necessarily a good measure of what is ethical*”.

Orphan devices

The National Insurance Act⁴²⁶ (folketrygdløven) gives rights for the use of assistive devices (orphan and common) for daily life activities and work.

Specialised social services

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 a rare disorder and their families receive treatment, care and services appropriate to their needs within their local community.

Frambu⁴²⁷ 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.

2.4. 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 alliance⁴²⁸

⁴²⁵ <http://www.ncbi.nlm.nih.gov/pubmed/20861122>

⁴²⁶ <http://www.lovdatab.no/all/hl-19970228-019.html>

⁴²⁷ <http://www.frambu.no/>

⁴²⁸ http://www.orphanet.ch/PDF/MEDIENMITTEILUNG_Gruendung_IG_Seltene_Krankheiten_f_def.pdf

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 (*JG rare diseases*) is actively engaged in advocating the development of a national action plan for the country's rare disease patients.

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.

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 expertise⁴²⁹. 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 medullary tumours, surgery of epilepsy and neurosurgery of complex vascular anomalies of the central nervous system.

Pilot European Reference Networks

Switzerland has participated and participates in the following European Reference Networks for rare diseases: Dyscerne, E-IMD, ENERCA, EPI/EPNET and PAAIR.

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.

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 authorisation⁴³⁰ 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

⁴²⁹ <http://www.gdk-cds.ch/index.php?id=903&L=1>

⁴³⁰ Federal Act on Human Genetic Testing (HGTA) of 8 October 2004, <http://www.admin.ch/ch/e/rs/8/810.12.en.pdf>

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 296 genes and an estimated 320 diseases in the Orphanet database⁴³¹; 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, ProRaris⁴³², 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 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 program⁴³³ 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.

As a patients’ 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 organize, 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) in their country for entry into the Orphanet database. In 2011 the team launched the Orphanet Switzerland national website⁴³⁴ 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.).

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 president of 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.

⁴³¹ Information extracted from the Orphanet database (September 2011).

⁴³² www.prorarais.ch

⁴³³ « Too expensive: you die ! »: <http://www.tsr.ch/emissions/36-9/3264987-trop-cher-tu-meurs.html>

⁴³⁴ <http://www.orpha-net.ch/?lng=FR>

Help line

There is currently no help line available for rare diseases in Switzerland.

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.⁴³⁵

Good practice guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

National rare disease events in 2011

To mark Rare Disease Day 2011, the first conference on rare diseases in Switzerland was organised on 19 February 2011 in Bern by ProRaris, the new Swiss Alliance, and by Orphanet Switzerland. Around 450 participants, including patients, health professionals, scientists and politicians, met to learn, share and discuss the rare diseases public health issue.

Telethon Switzerland is a regular, annual fixture and organised a fund raising event at the start of December 2011 for rare diseases.

Hosted rare disease events in 2011

A number of rare disease related events were organised in Switzerland in 2011: Treat-NMD Global Conference (8-11 November 2011, Geneva), Society for the Study of Inborn Errors of Metabolism – Annual Symposium 2011 (30 August – 02 September 2011, Geneva), 2nd Annual World Orphan Drug Congress (29 November – 1 December 2011, Geneva), Sanfilippo Foundation Switzerland International Congress (8-10 December 2011, Geneva).

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).

The *Gebert Rűf Foundation*⁴³⁶, a Swiss grant programme specifically for rare diseases, announced its third call for projects in 2011. 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. In 2009, the chosen topics were: Preventing Nodule Formation in Hyaline Fibromatosis Patients; Genetic Screening for Disease-Causing Mutations in Familial Polycythemia Using Next Generation DNA Sequencing; Gene Hunting for Recessive Hereditary Peripheral Neuropathies by Recent and Highly-Parallel Technologies; Hereditary Sensory Neuropathy Type 1 - Pathomechanism and Therapy; and Identification of New Factors Implicated in Genetic Gonadal Disorders. In 2010, the chosen topics were: Towards a better mechanistic understanding of Friedreich's Ataxia; Role of macroautophagy in CGD and correction of the defect; Consanguinity and rare recessive disorders; Rescue of dysfunctional RNA processing in spinal muscular atrophy through PGC-1-alpha; and Novel mechanisms causing Lafora disease.

⁴³⁵ <http://www.bag.admin.ch/themen/medizin/00683/02724/03677/index.html?lang=de>

⁴³⁶ <http://www.grstiftung.ch/en.html>

⁶ <http://www.blackswanfoundation.ch/>

In 2011, the chosen topics were: Prodrug Platform for Rare Colonic Diseases; Treatment for Dysferlinopathies; Vaccination for the Prevention and Cure of Inflammatory Bowel Disease; Host- and Pathogen-Derived Factors in Chronic Mucocutaneous Candidiasis; Rational Targeting of FOXC2 Haploinsufficiency; and Role of snoRNAs in the Development of Prader Willi Syndrome. 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.

Participation in European research projects

Switzerland participates or has participated in European rare disease research projects including: AAVEYE, ANTIMAL, AUTOROME, BIOMALPAR, CLINIGENE, CSI-LTB, CSI-LTB, E-IMD EMVDA, EURADRENAL, EURO-LAMINOPATHIES, EUGINDAT, EURAPS, EUREGENE, EURO BONET, EURO GENTEST, EURO GLYCANET, EUROPEAN LEUKEMIA NET, EVI-GENORET, GENESKIN, GEN2PHEN, HDLOMICS, HUMALAB, IMMUNOPRION, LEISHMED, LYMPHANGIOGENOMICS, MYELINET, MILD-TB, MPCM, MYORES, NEUROPRION, NANOTRYP, NOVSEC-TB, NM4TB, PEMPHIGUS, PULMOTENSION, 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 are not currently committed members of 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

At least 36 orphan medicinal products 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 benefit⁴³⁷.

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

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>

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.

Other initiatives to improve access to orphan medicinal products

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

No specific activity reported.

2.5. 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 individuals⁴³⁸.

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 budget⁴³⁹.

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 actions⁴⁴⁰.

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.

⁴³⁸ 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>)

⁴³⁹ Notification regarding the Pricing of Medicinal Products for Human Use

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⁴⁴⁰ Turkey Health Transformation Program

(<http://www.saglik.gov.tr/EN/BelgeGoster.aspx?17A16AE30572D313AAF6AA849816B2EF1DACD7356F6C2568>)

<http://www.orpha.net/actor/EuropaNews/2009/doc/TurkHealthPolicy.pdf>

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 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, TREAT-NMD and EURO CARE 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.

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 98 genes and an estimated 140 diseases in the Orphanet database⁴⁴¹.

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 website⁴⁴² in the Turkish language. The team organised the 6th Eastern European

⁴⁴¹ Information extracted from the Orphanet database (September 2011).

⁴⁴² <http://www.orpha.net/national/TR-TR/index/orphanet-t%C3%BCrkiye/>

Rare Disease Conference in Istanbul on 24-26 November 2011 and the 1st National Rare Disease Symposium in Istanbul on 27 November 2011.

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.

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 2011

A press bulletin was released for Rare Disease Day 2011. Many web based media portals, daily journals have mentioned the importance and the goals of Rare Disease Day. Orphanet Turkey was featured in four national TV channel programs in the same week. In addition, 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 2011

The Orphanet Turkey team organised 6th Eastern European Conference for Rare Diseases and Orphan Drugs: Rare Diseases Policy Development in Eastern European Countries, Istanbul, 24-26 November 2011. The team also organised 1st National Rare Disease Symposium in Istanbul on 27 November 2011.

Other hosted events announced in *OrphaNews Europe* include: the 12th International Conference on Thalassaemia and the Haemoglobinopathies (11-14 May 2011, Antalya) and the Ninth Hereditary Hemorrhagic Telangiectasia International Scientific Conference (20-24 May 2011, Antalya).

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, 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 the first two Joint Transnational Calls (JTC) of the E-Rare-1 project and the first JTC of E-Rare-2. 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. Turkey also participated in the 2011 3rd Joint Transnational Call and will support Turkish research teams in 3 of the selected consortia.

IRDiRC

Turkish funding agencies are not currently committed members of the IRDiRC.

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 Pharmaceuticals 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. The National Draft Guideline is ready to be put into force.

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 period⁴⁴³.

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 2011, 40 (72%) of the 61 designated and centrally authorised medicines under the EU orphan medicinal products legislation are accessible in Turkey⁴⁴⁴. Of these orphan medicinal products, 13 (30%) are licenced in Turkey and 30 (70%) are procured by pre-licencing procedures. 72 EU orphan medicinal products in Turkey are illustrated below.

Around half of the EU-authorized 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-authorized 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 medicinal products entering the Turkish market attain their prices up to a maximum of 5% over the price set in its country of origin. 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

⁴⁴³ Regulation on Licencing of Medicinal Products for Human Use

<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawid=226>

⁴⁴⁴ Source: 6th Eastern European Conference for Rare Diseases and Orphan Drugs: Rare Diseases Policy Development in Eastern European Countries, 26 November 2011, Istanbul.

treatment of diseases for which the aetiology is not clearly defined and those which affect no more than 1 in 100'000 individuals⁴⁴⁵.

Orphan medicinal product reimbursement policy

All orphan medicinal products entering the market are 100% reimbursed.

Other initiatives to improve access to orphan medicinal products

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.

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.

⁴⁴⁵ 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>)

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