



2011 REPORT
ON THE STATE OF THE ART OF
RARE DISEASE ACTIVITIES
IN EUROPE
OF THE EUROPEAN UNION COMMITTEE OF
EXPERTS ON RARE DISEASES

PART III : ACTIVITIES IN EU MEMBER STATES
AND OTHER EUROPEAN COUNTRIES

Joint Action to Support the Scientific Secretariat of the Rare Diseases Task Force/
European Union Committee of Experts on Rare Diseases (N° 2008 22 91)



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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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GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), formerly the Scientific Secretariat of the European Commission's Rare Diseases Task Force (RDTF), through the Joint Action to support the Scientific Secretariat of the former-RDTF/EUCERD (N° 2008 22 91), which covers a three year period (January 2009 – December 2011).

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 drugs up to the end of 2010. A range of stakeholders in each Member State 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 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 or national health authorities

The report is split into three parts:

- Part I: Overview of Rare Disease Activities in Europe and Key Developments in 2010
- Part II: European Commission and other European activities
- Part III: Activities in EU Member States and other European Countries

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 this 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, in addition to data provided by the EUROPLAN associated and collaborating partners in response to the EUROPLAN questionnaire, past reports published by the European Commission (including past reports of the working groups of the Rare Diseases Task Force and EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan drugs, 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).

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

- **OrphaNews Europe**

Data from the OrphaNews Europe⁵ newsletter for the period 2007-2010 was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the 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.

- **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 2005*⁷ 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 2006*⁸, as well as the *RDTF Final Report – State of the Art and Future Directions – March 2008*⁹.

- **EUCERD Publications**

Parts II and III of this report presents an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*¹⁰ (July 2010). The methodology for the production of this previous report is outlined in the introduction. Information on the state of the art of centres of expertise at MS level was also collected during the EUCERD workshop on national centres of expertise and ERNs for rare diseases (8-9 December 2010¹¹ and 21-22 March 2011¹²).

- **Minutes of the EUCERD**

The minutes of the first meeting of the EUCERD held on 9-10 December 2011 (and previous minutes of the RDTF meetings) was 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 2010.

- **Reports on orphan drugs**

The information provided for each Member State concerning the state of affairs in the field of Orphan Drugs is taken, when referenced, from the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹³ 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*)¹⁴. 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*

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

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

⁷ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

⁸ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

⁹ <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

¹⁰ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

¹¹ <http://www.eucerd.eu/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf>

¹² <http://nestor.orpha.net/upload/file/EUCERDReport220311.pdf>

¹³ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

¹⁴ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*
http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

Comparative Study of Selected European Countries (No. 52 October 2009)” also provided information on orphan drug availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. 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 patient organisation alliances**

The site of 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 2010 site¹⁸, maintained by Eurordis, also provided information on events at Member State level¹⁹ concerning Rare Disease Day.

- **EUROPLAN questionnaire to collect information on rare disease activities**

In the context of the European Project for National Plans Development (EUROPLAN), the partners of the project (who include representatives of national health authorities, expert researchers and clinicians, national alliances of rare disease patient organisations from all MS, and a number of other experts from national health authorities) were addressed a questionnaire and asked to provide detailed information, especially information from sources in their languages, which is more difficultly accessible on the state of rare diseases activities in their country. The structure of the questionnaire (a sample of this questionnaire is included in Annex IV of the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*²⁰) followed the structure of the Commission Communication on an action in the field of rare diseases²¹: 19 main questions were formulated in order to collect key data on a number of actions in their country. Since the detail of the answers to these questionnaires varied depending on the information available and the actions specific to the Country, a session of telephone interviews was also carried out to improve the information available, where appropriate. The collection of the information was concluded in October 2009.

- **EUROPLAN national conferences final reports**

In the context of the EUROPLAN project, 15 national conferences were organised in collaboration with Eurordis and national rare disease patient alliances in 2010 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 diseases²² and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports²³ 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 exploited 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

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.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

²¹ Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on “Rare Diseases: Europe's challenges” (COM(2008) 679 final)

²² http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf

²³ <http://www.eurordis.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports>

disease research projects, registries, clinical trials and rare disease/orphan drug policies outside of Europe for Part I. Orphanet also provides links²⁴ 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 project²⁵, in particular the report *Rare diseases research, its determinants in Europe and the way forward*²⁶ 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 conferences, as well as participation in Rare Disease Day events and partnerships. This surveillance at national level was exploited to provide information for the events section for each Member State.

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

2. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides a compilation of information from the previous report 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*) elaborated in 2010, which has been updated in 2011 to take into account advances and activities in the field of rare diseases and orphan drugs at EU and MS level in 2010.

Although, in the previous report, information was structured to provide a retrospective of actions at EU level and the state of affairs in the field in each EU Member State (i.e. pre-2009), as well as an inventory of initiatives and incentives undertaken in 2009 at EU and MS level, it was decided in consultation with the EUCERD to take a different approach to this year's report. The current report has merged the information from 'retrospective' and '2009' sections of the previous report and updated it to provide an overview of the state of the art of rare diseases activities in Europe which takes into account the advances up to the end of 2010 whilst providing background information to set these activities in context in order to provide a view of the evolution of activities. The EUCERD also decided that this year's report should include a shorter overview of EU and MS activities in the field of rare diseases (Part I) in addition to the broader 'background' document (Parts II and III).

Once this information was merged and updated using the sources cited above, a draft of each country section was sent in April to a range of key stakeholders in each respective country for their input along with a guidance document providing an explanation of the type of information to include if available for each category. The stakeholders identified for each country included: the MS representatives at the EUCERD and their alternates, the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, the partners of the E-Rare consortium, MS representatives on the COMP, representatives of national competent authorities and other rare diseases experts identified at national level. The collected feedback was integrated to the country reports to elaborate the final drafts which were sent at the end of May 2011 to the EUCERD MS representatives for their final validation, to the best of their knowledge, of the information concerning their respective country.

Part II 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, as well as the EMA: this process was carried out in May/June 2011 by the Scientific Secretariat of the EUCERD. The European Commission is not responsible, however, for the completeness and the correctness of the information presented in this report.

²⁴ http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

²⁵ <http://www.rdplatform.org/>

²⁶ http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

Part I was the last part of the report to be elaborated: the overview of the state of the art of rare diseases activities in Europe and key developments in 2010 is the result of an analysis of the information collected for Parts II and III. Part I was drafted by the Scientific Secretariat of the EUCERD before validation by the Bureau of the EUCERD acting as the Editorial Board for the present report.

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 as well as a short summary of key developments at EU and MS level in 2010; Part II concerns activities at EU level; Part III 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 the 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 is a list of contributors the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe and key developments in 2010 at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts II and III, 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 drugs and therapies for rare diseases, patient organisations and information services.

Part II of the report on activities at EU level is organised slightly differently to the last edition of the report where activities were presented in sections corresponding to the European Commission Directorates General (DG) of the European Commission implicated in the field of rare diseases. In the present report, activities concerning rare diseases and orphan drugs at EU level are 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 drugs and therapies for rare diseases
4. Other European rare disease activities (i.e. meetings at European level and selected transversal EU activities).

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 or 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.

The sub-section concerning EC activities in the area of orphan drugs and advanced therapies for rare diseases is organised accordingly: European legislation concerning orphan medicinal products and related activities, 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 drugs, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan drugs.

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 2010.

Part III concerns the activities in the field of rare diseases in each of the 27 Member States plus Norway and Switzerland as EEA 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 expertise²⁷
- Registries
- Neonatal screening policy
- Genetic testing²⁸
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines;
- Best practice guidelines
- Training and education initiatives
- Europlan national conference
- National rare disease events in 2010²⁹
- Hosted rare disease events in 2010³⁰
- Research activities and E-Rare partnership
- Participation in European projects³¹
- Orphan drugs (Orphan drug committee, Orphan drug incentives, Orphan drug availability³², Orphan drug reimbursement policy, Other initiatives to improve access to orphan drugs, Orphan drug pricing policy)
- Orphan devices
- Specialised social services

The choice of categories of information for inclusion in this year's report were discussed by the EUCERD at their first meeting (9-10 December 2010): categories new to this year's edition include genetic testing, Europlan national conferences, orphan devices, other initiatives to improve access to orphan drugs and orphan drug pricing policy. The categories for which information is provided depends 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.

²⁷ The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

²⁸ This section contains data extracted in May 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).

²⁹ As announced in OrphaNews Europe.

³⁰ As announced in OrphaNews Europe.

³¹ Past and ongoing participation in pilot European Reference Networks, DG Research and Innovation financed projects, EUROPLAN and European registries. Some countries have added information on additional European projects.

³² Contacts were asked to provide information on availability of orphan drugs (i.e. which drugs are registered/marketed at national level): 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 to which of these concepts is being referred.

ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG- Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area (Iceland, Switzerland, Norway)
EMA - European Medicine's 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 Rare Diseases Patient Organisation
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
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

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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals. In the national plan of action (still under development; see below) it is foreseen to officially adopt the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

In May 2009, the highest advisory board ("Oberster Sanitätsrat") of the Austrian Ministry of Health (BMG) established a subcommittee ("Unterkommission") for rare diseases, consisting of 17 members from 13 different organisations or institutions (covering the main stakeholders in the field). This working group was headed and managed by the Austrian Orphanet team and was in charge to set the grounds for a national plan of action for rare diseases in Austria. It was the first time ever that an expert committee of this size, covering a broad spectrum of viewpoints, was working on rare diseases in such 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.

In its first sessions, the working group decided to adopt a step-by-step working strategy with the following deliverables:

- A general text document (the "framework" of the action plan, deliverable D1) containing:
 - i. a comprehensive introduction into the topic;
 - ii. the definition of approximately nine to ten strategic priorities covering the most relevant needs in Austria (titles only);
 - iii. a final section defining the general mode of monitoring.
- Detailed chapters for the key strategic priorities previously defined in the general text document (deliverables D2-D10/11).

It was further decided that, as soon as a draft for any of the chapters/deliverables is finished, this draft will be reviewed by the highest advisory board (see above) and, after approval, referred to the political decision process. This strategy was developed to ensure that:

- The final document fulfils the standards of a comprehensive plan of action;
- Individual priorities can be implemented as soon as possible without any delay caused by the elaboration of the other deliverables.

In the few following meetings, the committee worked on the content and the details of deliverable D1.

In the first meeting in 2010, the working group adopted the major parts of deliverable D1, i.e. the introductory part and the final definition of the strategic priorities covered by the national plan. While most parts were decided unanimously, single aspects with regard to the order of the strategic priorities were adopted with a qualified majority. The nine strategic priorities of the Austrian national plan of action are as follows:

- i) Recognition of the specificity of rare diseases;
- ii) Improving health care pathways by:
 - a) Defining and establishing specialised centres of expertise and centres of competence for groups of related rare diseases (see also chapter on "Centres of Expertise" below);
 - b) Establishing a national coordination centre for rare diseases (to administer and accompany, amongst other activities, the certification of specialised centres, as well as to establish and coordinate a national network of these centres);

- c) Establishing and sustaining support for a comprehensive information system for rare diseases (i.e. Orphanet in Austria);
- d) Establishing a central office for rare diseases;
- iii) Improving the diagnostic pathway and extending diagnostic capabilities/possibilities (including the development and clinical implementation of screening tests);
- iv) Improving therapeutic options/procedures and the access to therapy;
- v) Establishing selective research programmes specifically addressing rare diseases;
- vi) Improving awareness and knowledge about rare diseases (addressees: general public, health care personnel, professionals);
- vii) Improving the epidemiological knowledge on rare diseases (establishment of a national/cross-border registry);
- viii) Establishing a permanent expert group for rare diseases at the Austrian Ministry of Health;
- ix) Recognition of the attainments of patient support groups.

All members of the subcommittee agreed that out of these nine strategic priorities, the chapter on “Improving health care pathways” constituted the priority with the highest relevance, and that this chapter should therefore be elaborated first. Accordingly, in the three final meetings, the working group focussed on:

- (a) The adaption of the RDTF criteria for centres of expertise to the specific needs of a small to medium-sized country like Austria, considering in parallel the framework requirements (for instance pre-existing structures) in the healthcare system;
- (b) The development of a modular system of criteria defining expert clinics with outstanding ‘pure clinical’, as well as ‘combined clinical and scientific’ expertise;
- (c) The definition of a possible certification process for these types of expert centres;
- (d) The establishment of a national coordination centre with well-described first duties and responsibilities, as well as additional (optional) modules that might be relevant – and then implemented – in the future;
- (e) The functional integration of Orphanet Austria into this coordination centre in order to maximise the synergies between the two structures.

While the work on the criteria for the different types of expert clinics could not be finished within 2010, the establishment of a national coordination centre for rare diseases, and the functional integration of Orphanet into this centre, was eventually approved at the last meeting of the working group in November 2010.

The coordination centre was officially established on 1 January 2011 at the Austrian Health Institute; it is thus the first measure of the national plan that has been implemented (including the sustained funding of Orphanet as the national information system for rare diseases). In parallel, it is intended to be the main driving force to finish the elaboration of the national plan of action within the coming year.

In December 2010, the subcommittee for rare diseases was dissolved (as part of the *Oberster Sanitätsrat* that had finished its regular three-years-period). It will be replaced in 2011 by a new expert committee, affiliated directly to the Ministry of Health.

Centres of expertise

Currently, there are no officially designated centres of expertise in Austria; informally, 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 strongly supports the concept of such centres. It is therefore expected that further centres of expertise will be identified and that all these centres 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 the legal requirements, and to take into account pre-existing structures of the health care system, in Austria and integrated into the national plan of action for rare diseases, and (c) this national plan has been implemented successfully.

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

Registries

Currently, no nationwide, general, comprehensive registry for rare disease patients exists in Austria. Approximately 13 registries for individual rare diseases or groups of rare diseases are run by specialised clinics or networks of experts from different clinics. 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, EMSA-SG, EUROCAT and ENRAH. Actions in this area are included in the National Plan for Rare Diseases (“National/Cross-border registry”). The Austrian Ministry of Health did not have any budget in 2010 to financially support selected individual patient registries.

Neonatal screening policy

Since the early 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 diseases and conditions: adrenogenital syndrome, carnitine-acylcarnitine translocase deficiency, carnitine palmitoyltransferase I deficiency, carnitine palmitoyltransferase II deficiency, carnitine transporter defect, citrullinemia / argininosuccinate lyase deficiency, congenital hypothyroidism, cystic fibrosis, galactosaemia, glutaric acidemia type I, glutaric acidemia type II / multiple acyl-CoA dehydrogenase deficiency, homocystinuria and hypermethionemia, isobutyryl CoA dehydrogenase deficiency, isovaleric academia, β -Ketothiolase deficiency, long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency / trifunctional protein deficiency, maple syrup urine disease, medium-chain acyl-CoA dehydrogenase deficiency, methylmalonic aciduria / propionic academia, multiple carboxylase (holocarboxylase) deficiency, phenylketonuria and hyperphenylalaninemia, short-chain acyl-CoA dehydrogenase deficiency, tyrosinemia type I (II), very long-chain acyl-CoA dehydrogenase deficiency, 2-Methyl 3-hydroxy butyryl-CoA dehydrogenase deficiency, 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency, 3-Methylcrotonyl-CoA carboxylase deficiency, and 3-Methylglutaconic aciduria type I. This screening panel remained unchanged in 2010.

The scientifically based NBS for lysosomal storage disorders has been further developed since 2009 and now includes Mucopolysaccharidosis (MPS) type 1 disease in addition to the previous disorders (Gaucher, Fabry, Pompe, Nieman-Pick Type A/B). At end of 2010 it had not been decided whether (and when) any of these diseases should be included in the national program.

Genetic Testing

Molecular genetic testing in Austria is regulated by the so-called “Gentechnikgesetz” (GTG), first established in 1994³³ and last revised in 2005³⁴. 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 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”).

³³ http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/510_1994.pdf

³⁴ <http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/gtg-nov.11-05.pdf>

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 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 a hospital as an inpatient or (b) in an outpatient clinic or private practice (general practitioner or consultant of a specific medical discipline). 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 the basis of an average daily rate calculated for one patient in this specific hospital and department/clinic. However, hospitals have to make efforts to not exceed the budgets allotted to them for each calendar year. In the second case (outpatient clinic, private practice), reimbursement is the responsibility of the health insurance fund of the patient. In this instance, specific tariffs are calculated by the insurance fund for each type of service and services are reimbursed according to the tariff catalogue. Of note, only services that have been successfully negotiated with the insurance fund and integrated into their individual tariff catalogue are eligible for 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) insurance fund 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 inpatients, the hospital covers the costs according to the tariffs of the laboratory performing the test;
- (c) For outpatients, the respective insurance company carries the costs; however, it is possible that certain analyses (depending on the internal regulations of insurance fund) require an ex-ante approval by the head consultant (“Chefarzt”) of the insurance 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 have currently to be authorised by the “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 110 genes and an estimated 173 diseases in the Orphanet database³⁵.

National alliances of patient organisations and patient representation

To date, there is still no specific national alliance of patient organisations for rare diseases in Austria. Nevertheless, the situation has developed significantly within the past year.

Initiated and organised by the Austrian Orphanet team, representatives of the individual patient organisations participated in common activities and events during the past few years. Some highlights were the Rare Disease Day events and the first national congress for Rare Diseases in Mariazell (see below). This led to an increased confidence between the individual groups, as well as the growing awareness, that a common effort will be necessary to approach the general problems of rare diseases.

At the conference in Mariazell, patients and representatives of different patient organisations had the opportunity to experience the advantages, perspectives, and development potential that would be brought about by an active umbrella organisation using the example of EURORDIS, and to discuss this topic extensively. At the end of the conference, about 20 groups made an informal declaration of intent to establish a national alliance of rare disease patient organisations. Of note, the Pharmig, one of several associations of the Austrian pharmaceutical industry, stated their intention to participate as one possible partner, amongst others, in the core funding of this national alliance.

Apart from this group effort dedicated specifically to rare diseases, general alliances of patient organisations (both for rare and non-rare diseases) do exist on the state level (ARGE Selbsthilfe Carinthia, Upper Austria, Lower Austria, Salzburg, Styria, Tyrol, Vorarlberg, and Vienna). They are united under the supra-

³⁵ Information extracted from the Orphanet database in May 2011.

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. Very recently, the Austrian Ministry of Health decided to structurally support the *ARGE Selbsthilfe* by providing an office (including one secretary position) from pre-existing resources of the Austrian Health Institute (GÖG). Apart from that, for the near future, no further specific support of rare disease patient organisations is planned by the ministry.

Further institutions supporting patient organisations for non-rare, as well as rare diseases (all located in Vienna) are the *Selbsthilfe-Unterstützungsstelle für gesundheitsbezogene Selbsthilfegruppen (SUS)* and the *Martha-Frühwirt-Zentrum*. The SUS (as part of the Fonds Soziales Wien) provides all kinds of administrative support, but does so without funding; similarly, the Martha-Frühwirt-Zentrum offers administrative support and rooms or offices for the activities of patient organisations, but again without direct funding.

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”.

Already in 2009, representatives of two rare disease patient organisations were mandated - during a meeting of active and interested patient organisations in the rare disease field – to represent patients in the subcommission for rare diseases and to take part in the development of the national plan of action. When the subcommission will be replaced in 2011 by a new expert committee which will be directly located at the Ministry of Health (see above), the number of patient representatives will be increased (in parallel to the number of medical specialists).

Sources of information on rare diseases and national help lines

Orphanet activities in Austria

Since 2002 there is a dedicated Orphanet team in Austria, currently 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 team was designated in 2010 as the national Orphanet team for Austria by the Austrian Ministry of Health, as was a second new team at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG). 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 2010, the Austrian country team continued to finance and maintain a self-developed country website, launched back in 2008, in order 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. To this end, the team reported about major events and activities, like the rare disease day 2010 or the national congress on rare diseases in Mariazell (see below), organised either by Orphanet Austria itself or by other stakeholders. As a new web tool, an interactive forum on rare diseases was developed and integrated into the country website intended as one national discussion platform on rare diseases; however, this tool has been used only sporadically despite several attempts to motivate in particular patients to exchange their knowledge, views and questions about (specific) rare diseases. In 2011, a new Orphanet country site, adapted to the new common layout of Orphanet country websites, will be developed as soon as the Joint Action Orphanet Europe has started.

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 was established at the Austrian Health Institute (as part – and first structural measure – of the national plan of action), financed by the Austrian Health Ministry. Orphanet Austria was integrated into this coordination centre to enable maximum synergy between the two structures.

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. The helpline is operated by two physicians and can currently be contacted on one afternoon per week. Although announced locally, it can of course be contacted from all around the country. According to the information available, it is funded on a private basis.

Other sources of information

Further sources of information on rare diseases include:

- Disease-specific websites of patient organisations. A number of patient organisations for specific rare diseases – or groups of rare diseases – exist in Austria that host excellent websites providing extensive and very detailed information on “their” rare disease/group of rare diseases (including information on the medical background, symptoms, diagnostics and treatment/care of patients);
- Some medical departments also host websites with comprehensive and useful information on those rare diseases they are focussing on;
- Further websites, under development in 2010, will go online during the next year.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

The academy of the Epidermolysis Bullosa (EB) House hosts training workshops for epidermolysis bullosa on a regular basis. In addition, the Department of Dermatology of the private Paracelsus Medical University in Salzburg participated in the GENESKIN project in 2010, organising courses on rare genetic skin diseases. The 1st Mariazeller Gesundheitsdialog (see below) covered rare diseases from several medical disciplines (dermatology, immunology, haemato-oncology, haemophilia, infectiology, cardiology, nephrology/andrology, pulmonology, and paediatrics/metabolic disorders) and was approbated by the Austrian Medical Association as a 7 hour training-seminar.

Europlan national conference

Austria did not hold a Europlan national conference in 2010.

National rare disease events in 2010

The central rare disease event in Austria was the 2nd Austrian March for Rare Diseases held in Vienna on February 27, 2010. Approximately 350 participants - patients, physicians, researchers, supporters, representatives of the biomedical industry - came together to raise awareness of rare diseases. This year, the route led through the inner city of Vienna from the Opera house to the Hofburg castle. The march was followed by a closing event with lunch buffet and speeches. The event was widely covered by the media.

On February 28, the 2nd Rare Diseases Information Day took place in Salzburg. It was organised and supported by several patient organisations.

On June 11, 2010, the first Regional Forum on Rare Diseases took place in Salzburg, organised by the university departments of dermatology and paediatrics and adolescent medicine, the International Forum Gastein, along with the newly founded Institute for inherited metabolic disorders. It comprised lectures on the interdisciplinary challenge of rare metabolic disorders, the orphan drug legislation, and Orphanet as an information platform. Several experts, primarily from the private Paracelsus Medical University Salzburg, reviewed their specialties with a particular focus on selected rare diseases or groups of rare diseases. The meeting finished with a lively panel discussion on the situation of rare diseases in Austria, focusing on current difficulties and potential solutions with a particular focus on the establishment of certified centres of competence and on reimbursement policies.

On June 12, 2010 a regional symposium was held in Vienna with the topic “10 years of enzyme replacement therapy for Anderson-Fabry disease”.

The Mariazeller Gesundheitsdialog under the scientific auspices of Orphanet Austria (Mariazell, October 15-16, 2010) was entirely dedicated to the field of rare diseases. It was the first national congress on rare diseases in Austria that brought all the different stakeholders in the rare disease field (physicians and scientists, patients and patient organizations, politicians, health care and social welfare representatives, pharmaceutical industry) together for a common dialogue. There were three key aspects: 1) for physicians: a training program on rare diseases from different medical disciplines (see above); 2) for patients: apart from lectures on patients’ rights, fund raising, and conflict management, the most important part was the introduction of EURORDIS as an excellent example of a well organised umbrella organisation, followed by an intensive discussion; and 3) introduction of the EU-initiative for a national action plan and the state of play regarding its implementation in Austria; the highlight was a mixed panel and plenary discussion with all participants.

Hosted rare disease events in 2010

Austria did not host any international rare disease related events in 2010.

Research activities and E-Rare partnership

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 Bürgermeister 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, eventually resulting in 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, some fundraising patient organisations finance rare disease research projects. One strategic priority in the Austrian national plan will be the implementation of a defined, separate funding budget in the main existing research bodies, which will be specifically dedicated for research on rare diseases, as aforementioned in the National Plans segment (“Establishing a selective funding for research on rare diseases”).

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)*³⁶ 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 will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Austrian teams participate, or have participated, in the following European Reference Networks for rare diseases: EUROHISTIONET, NEUROPED (main partner), Paediatric Hodgkin Lymphoma Network and PAAIR. Austrian teams participate, or have participated, in European research projects for rare diseases including: BNE, CLINIGENE, EMSA-SG, EMINA, ENRAH, ENCE-PLAN, EURIPFNET, EUROTRAPS, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EURO-IRON1, GENESKIN, LYMPHANGIOGENOMICS, MYELINET, NEUTRONET, NEUROPRION, PERXISOMES, PNSEURONET, PROTHETS, PULMOTENSION, PWS, RHORCOD, RD PLATFORM, SIOPEN-R-NET and SARS/FLU-VACCINE. Austrian teams contribute to the following European registries: AIR, EUROCARE CF, EMSA-SG, EUROCAT and ENRAH. Austria contributes to the EUROPLAN project. Austria is part of the SIOPEN-R-NET research network. In addition, Austrian experts are represented in initiatives on the field of orphan drugs lead by the European Commission DG Enterprise.

Orphan drugs

Orphan drug committee

There is currently no committee for orphan drugs in Austria.

Orphan drug incentives

According to information collected for the publication of the first “*Inventory of Community and Member States’ incentive measures to aid the research, marketing, development and availability of orphan medicinal products*” the Austrian Drugs Act (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)*”³⁷.

Orphan drug availability

As soon as marketing authorisation is provided, orphan drugs are available quite quickly in Austria (regarding possible delays in the provision of orphan drugs see below in the chapter on reimbursement policy). Actions

³⁶ <http://www.fwf.ac.at/>

³⁷ *Inventory of Community and Member States’ incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p7).*

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 improve availability. However, any kind of off-label use is not well accepted by public authorities in Austria.

Orphan drug 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 reasonable³⁸. Contract physicians are entitled to prescribe all medicines included in the Austrian Reimbursement Code (EKO)³⁹ - 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 online tool. A reply is sent within 30 minutes. 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.

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 three 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 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 2009 public expenditure per prescription for orphan drugs amounted to €2,754 and in 2010 to €2,771, which is a 0.67% rise. Altogether the Austrian Social Insurance spent €85 million on orphan drugs in 2010.

Other initiatives to improve access to orphan drugs

No specific information reported.

Orphan drug pricing policy

In case a marketing authorisation holder applies for reimbursement in Austria, the product falls under statutory price regulations. This means that the maximum reimbursement price may not exceed the EU-25 average price; in most cases this price is subject to negotiations between the main Association of Austrian Social Security Institutions and the marketing authorisation holder. In case the product is not reimbursed the price of the product can freely be set by the manufacturer. Unauthorised orphan drugs may be imported on case-by-case decisions. The majority of orphan drugs are dispensed in hospitals.

Orphan devices

No specific information reported.

Specialised social services

No specific activity reported.

³⁸ Art. 133 ASVG 1955, regulating the extent of medical treatment [Art. 133 ASVG 1995; BGBl. No. 189/1955]

³⁹ Art. 31.3(12) ASVG, on the publication of the Reimbursement Code EKO (Art. 31.3(12))

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 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 of the need to development a specific National Plan for Rare Diseases was highlighted.

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 drugs. The Fund for Rare Diseases and Orphan Drugs, managed by the King Baudouin Foundation, is financially supported since 2009 within the framework of a 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, and administration participated in the working groups of the Fund for Rare Diseases and Orphan Drugs that are actually finalising the development of a set of recommendations grouping specific measures into different domains.

The development of these recommendations is elaborated in two phases:

- Phase 1 concerning 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 concerning 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 work on the second phase of the strategy is nonetheless progressing. The final plan with the adaption and actualisation of the recommendations of phase 1 and the integration of this revision of phase 1 with the recommendations of phase 2 will be sent to the minister of Social Affairs and Public Health at the end of the first semester of 2011. The recommendations concerning phase 1 are available for consultation in Dutch, French and English online⁴⁰.

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 drug costs). Nevertheless, most of the expenditures for rare diseases are covered by the general health system budget. 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.

The future mentioned plan for rare diseases must address additional actions which are needed to take into account the specificity of rare diseases in addition to those actions foreseen in the National Plan of Chronic Diseases and the National Cancer Plan (both plans exist already in Belgium).

⁴⁰ <http://www.kbs-frb.be/publication.aspx?id=271066&LangType=2060>

In other actions related to rare diseases, genetic counselling, carried out by a multidisciplinary team, will be financed through a convention with the 8 Belgian genetics centres. Requirements of quality are included in the convention: to enforce guidelines and recommendations, internal assessment of quality, participation in EuroGentest controls, etc.

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 NIHDI and work under a convention. These centres include: the centres for human genetics, 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 the 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.

Registries

Belgium contributes to European registries including EUROCAT, AIR, ECFS, RBDD, ESID, ENRAH, EUNEFRON and EURECHINOREG. In addition, Belgium has some national and regional registries for specific rare diseases, or groups of diseases such as cystic fibrosis and neuromuscular diseases.

There are at this moment two problems with the existing registries. First, a central entry point is needed to increase the validity of the existing registries and second not all rare diseases are covered by the existing registries. Therefore, in order to account for these difficulties, a budget of €129'000 is foreseen in 2011 for the preparation of a conceptual note concerning the creation of a Central National Registry of Rare Diseases.

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 by three recognised centres for following 11 metabolic diseases: phenylketonuria/hyperphenylalaninemia, congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, medium-chain acyl-CoA dehydrogenase deficiency (MCAD), multiple acyl-CoA dehydrogenase deficiency (MADD), glutaric acidemia type I, isovaleric acidemia, maple syrup urine disease (leucinosis), propionic acidemia and methylmalonic acidemia. In the French community neonatal screening is provided for 6 metabolic diseases: phenylketonuria, congenital hypothyroidism, maple syrup urine disease (leucinosis), galactosaemia, tyrosinemia and homocystinuria. In addition, a specific screening for the risk group for thalassemia is organised by the Brussels Capital Region.

Genetic testing

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

All genetic centres have or are in the process of obtaining a certification and accreditation. 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 counselling 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.

A new nomenclature is in preparation with more tests on the list and a clear wording. The new nomenclature will thus be more transparent. A budget of €36 million euro is devoted to genetic testing.

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 (budget: €550'000). A list of authorised tests and the foreign reference laboratories is in preparation.

Diagnostic tests are registered as available in Belgium for 344 genes and an estimated 375 diseases in the Orphanet database⁴¹.

⁴¹ Information extracted from the Orphanet database in May 2011.

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 80 patient organisations for rare diseases in Belgium and is affiliated with Eurordis. RaDiOrg.be organises the Rare Disease Day and receives funding for this event, in particular from the federal government and the Belgian pharmaceutical industry umbrella group Pharma.

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 that an observatory on chronic diseases will be created including patient organisation representatives and health insurance representatives in order to advise the National Institute of Reimbursement on all issues concerning accessibility of care for chronic 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 exists of two taskforces: (1) a scientific taskforce and a consultative taskforce.

Sources of information on rare diseases and national help lines

Orphanet activities in Belgium

From 2001 - 2011 there was a dedicated Orphanet team in Belgium, hosted by the Centre of Human Genetics at the Catholic University of Leuven. From April 2011 onwards, a national Orphanet team for Belgium has been designated by the Federal Public Service Health, Food Chain Safety and Environment at the Scientific Institute for Public Health. The Federal Public Service Health will also participate in the 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 has signed a convention with the Scientific Institute of Public Health (€129'000) for the preparation of a conceptual note on the development of a register of rare diseases and for the national support for the Orphanet database as proposed in the Belgian National Plan for Rare Diseases. The mentioned budget mainly concerns the Dutch translation of the Orphanet database in order to increase the linguistic accessibility for Belgium's population.

Official information centre for rare diseases

There is no official information centre or website on rare diseases other than Orphanet. A budget of €100'000 is foreseen for the creation of a national portal with national information concerning for example the accessibility to orphan drugs and treatment for patients with rare diseases and reimbursement issues. The users of this information portal will be patients, healthcare professionals and citizens.

Help line

There is currently no rare diseases help line in Belgium, although the feasibility of running a rare diseases helpline is under discussion within the framework of the proposition of the Belgian National Plan of Rare Diseases by the Fund for Rare Diseases and Orphan Drugs.

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) maintains an interactive website in collaboration with Pharma.be and the Belgian ethical committees, aimed at ethical committees, industry and the FAMHP in order to provide on line registration, approval and follow-up of clinical trial dossiers in Belgium. The website is in a test phase. The FAMHP also intends to develop a Belgian website/portal for the general public in the future. The site would be similar to the European IFPMA-portal and will be in line with the transparency position with relation to clinical trials⁴².

The Fund for Rare Diseases has contacted representatives of different university hospitals to initiate a common strategy to collect information on the number of rare disease patients and treatments. Scientific

⁴² "Joint Position on the disclosure of clinical trial information via clinical trial registries and databases", 10 November 2009, www.ifpma.org/clinicaltrials.

board meetings for the Belgian Orphanet site started in 2008 to validate the data already gathered on the existing rare disease services and research activities in Belgium.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

Europlan national conference

Belgium did not organise a Europlan national conference in 2010.

National rare disease events in 2010

The annual Rare Disease Day was held on 27 February 2010, organised by the Belgian umbrella organisation for rare disease patient organisations, RaDiOrg.be. During the day several presentations were given by stakeholders concerning the state of advancement by the fund for the recommendations and proposition for a Belgian National Plan for Rare Disease. Participants included politicians, academics, specialists, patients, industry etc. RaDiOrg.be also organised an awareness raising campaign for the day using the symbol of the Edelweiss, known as a rare plant. The first Edelweiss prize, rewarding the most promising young researcher in the field of rare diseases, was awarded to Lies Rombaut for her research on the quality of life of Ehlers-Danlos HT syndrome patients.

Hosted rare disease events in 2010

On 1 March 2010 E-Rare and Eurordis organised a symposium at the 'Centre de Presse Internationale' in Brussels entitled: "Bridging Patients and Researchers - To Build the Future Agenda of Rare Disease Research in Europe". Over 100 participants came together at this event to discuss determinants of rare disease research, obstacles and solutions.

Amongst the rare disease events hosted in Belgium this year and announced in *OrphaNews Europe* were: Designing the Future Conditions for Clinical Research in Europe Workshop (17 March 2010, Brussels); 18th International Workshop on Vascular Anomalies (21-24 April 2010, Brussels); 22nd Annual Meeting of the European Academy of Childhood Disability (27-29 May 2010, Brussels); the Progress in Paediatric Neurology Research Conference (1-2 October 2010, Leuven); Optimising Orphan Drug Development (15-16 November 2010, Brussels); Second Workshop on Patient Engagement in HTA (17 November 2010, Brussels).

Research activities and E-Rare partnership

Research activities

There are no specific research programmes for rare diseases in Belgium. The FNRS (National Fund for Scientific Research)⁴³, however, provides funding for applied research on rare diseases and has also created a contact group to foster public information. Rare disease research also benefits from initiatives such as programmes to stimulate translational R&D. Some fundraising patient organisations also finance rare disease research.

E-Rare

The FNRS is a full, contracting member, of the E-Rare consortium, participating in the whole decision and implementation process of E-Rare although Belgium did not participate in E-Rare's first two Joint Transnational Calls. The Research Foundation Flanders (FWO)⁴⁴ and Fund for Scientific Research (FNRQ) will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

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. 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, EURO CARE-CF, EUROSCA, EVI-GENORET, FASTEST-TB, EUNEFRON, EUROAGENTEST, EUROGLYCANET, GENESKIN, GEN2PHEN, HUE-MAN, KALADRUG-R, LEISHMED, IMMUNOPRION, MITOTARGET, MYASTAID, NANOTRYP, NEOTIM,

⁴³ www.frs-fnrs.be

⁴⁴ www.fwo.be

NEUROPRION, PEROXISOMES, PULMOTENSION, PWS, RATSTREAM, RD PLATFORM, SIOPEN-R-NET, STEM-HD, TB-DRUG OLIGOCOLOR and WHIPPLE'S DISEASE. Belgian teams contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, ENRAH, EUNEFRON and EURECHINOREG. Belgium contributes to the EUROPLAN project.

Orphan drugs⁴⁵

Orphan drug 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^{46,47} on orphan drugs 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 drugs. 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 drugs and rare diseases and to develop strategic solutions.

Orphan drug incentives

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

Orphan drug availability

Since 2001, orphan drugs 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.

Orphan drug 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"⁴⁸.

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 drugs 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 drugs. A decision on the reimbursement is taken within 180 days following the submission of the reimbursement request.

At the end of December 2010, 48 orphan drugs were eligible for reimbursement in Belgium (including two products that do not have EMA orphan drug status, but that are reimbursed for an orphan indication) for a total of 54 orphan indications⁴⁹. Orphan drugs 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 Drugs reimbursed by the NIHDI⁵⁰ includes: Afinitor, Aldurasyme, Atriance, Benefix, Busilvex, Carbaglu, Cystadane, Diacomit, Duodopa, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyf, Flolan, Gliolan, Glivec, Increlex, Kuvan, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Replagal,

⁴⁵ 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).

⁴⁶ <http://www.weesziekten.be/symposiumfr.htm>

⁴⁷ <http://www.maladiesrares.be/symposiumfr.htm>

⁴⁸ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p8).

⁴⁹ *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (p39).

⁵⁰ http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/OrphanCns.asp (updated 01/04/2010)

Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tasigna, Thelin, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Xagrid, Xyrem, Yondelis, Zavesca.

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 2010, there were 27 colleges for 44 orphan drugs. 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 months⁵¹ and can be renewed.

A study entitled "*Policies for Orphan Diseases and Orphan Drugs*⁵²", 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 drug reimbursement policy with other countries, estimates the current budget impact of orphan drugs, forecasts the expected future budget impact, and offers recommendations for policy makers concerning orphan drugs.

Other initiatives to improve access to orphan drugs

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)⁵³. A last possibility for non-reimbursed pharmaceutical products is reimbursement by the Special Solidarity Fund (SSF). Conditions for Compassionate Use or reimbursement through the SSF are defined by law. In 2007, orphan drugs accounted for about 35% of the SSF's total budget.

Orphan drug pricing policy

No specific information reported.

Orphan drug 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*⁵⁴ and is the first study of its kind to measure the impact of orphan drug expenditures on a country's overall medicinal product budget. Determining the total orphan drug costs in Belgium in 2008, the authors then forecast the impact over the next five years. Using multiple sources, the authors calculate that orphan drug 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 authorization 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 drugs 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 drug 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.

⁵¹ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp43-44).

⁵² Link to the report: http://www.kce.fgov.be/index_en.aspx?SGREF=5211&CREF=13651

⁵³ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p40).

⁵⁴ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=20482245

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 social plan for the financing of respite care structure for patients with rare diseases. Governmental measures for the integration of handicapped persons already exist in Belgium by means of social and financial support.

1.3. BULGARIA

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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

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

A National Consulting Council on Rare Diseases 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 covering 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 Ministerial Order 34 for expensive treatments and the National Health Insurance Fund.

The First National Conference for Rare Diseases in Bulgaria (28 to 30 May 2010)⁵⁵, organised within the scope of the Europlan project, brought together stakeholders in order to discuss the provisions of the plan and its implementation (see section "Europlan national conference" for more information).

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,

⁵⁵ <http://www.conf2010.raredis.org/>

thalassemia major, Gaucher disease and neuromuscular diseases. Treatment with orphan drugs is currently reimbursed in these centres, which also manage the provision of very expensive orphan drugs. 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 on national level: the centres will be distributed geographically equally in the country and will deal with all rare diseases.

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

Registries

Five nation-wide epidemiological registries concerning rare diseases have been identified: National Registry of Patients with Thalassemia Major, National Registry of Chronic Myeloid Leukaemia Patients, National Registry of Crohn Disease Patients, National Registry of Wilson Disease Patients and the National Cancer Registry. Bulgaria also contributes to the EURO CARE CF and TREAT-NMD European registries.

A preliminary version of an official list of rare diseases is being prepared, and following this an official registry for rare diseases should be set up.

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 "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, Transfusion Haematology and regional transfusion haematology centres in Bulgaria and patient organisations. Its main purpose is to create an epidemiological tool for identifying and tracking each patient. The registry will help doctors, researchers and health authorities to determine prevalence, morbidity, long-term outcomes and quality of life of the Bulgarian patients with thalassemia major. Moreover, this experience can be used as a model for creation of registries for other rare diseases. The second phase of the project was successfully completed in October 2010: this stage was aimed at updating the information on patients who were registered during the first phase of the project and to register newly diagnosed and not yet registered patients with thalassemia major. The results were discussed and adopted as official for the country at a workshop of the expert group on thalassemia, held in Varna in November 2010. A subsequent update and collection of new epidemiological data in will be organised in March-April 2011.

Following this very successful model, BAPES has initiated recently 3 new rare diseases registries. At the end 2010 the National registry of Chronic Myeloid Leukaemia patients was set following the outcomes from a pilot study in 2009 and a survey one year later. In early May the first results from a joint study of BAPES and Wilson disease patient association will be published. The Crohn Disease National Registry is already working and its statistics are scheduled to be officially adopted in June 2011. All BAPES-managed epidemiological registries for rare diseases involve joint activities by all stakeholders.

Rare tumours are included in the National Cancer Registry.

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.

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) Since 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 database⁵⁶.

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 national patient organisations in Bulgaria, such as the NAPRD. 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.

Roundtable discussions on the role of patient organisations' in health policy making were held on 29 October 2010 in Plovdiv, organised by the National Alliance of People with Rare Diseases (NAPRD), Bulgarian Association for Promotion of Education and Science (BAPES) and the Italian-Bulgarian Foundation – Plovdiv. Patient organisations, medical professionals, representatives of state institutions and the pharmaceutical industry attended the meeting. Patient associations asked for more power for their representatives to the public health bodies in order to play a really active role in rare diseases policy making, not only to be passive observers.

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

ICRDOD⁵⁷ is a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES⁵⁸) - 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. In November 2010 a review was published of the actual situation and tendencies in the rare diseases field in Bulgaria⁵⁹. It contains 5 main chapters: methodology and governance of the Bulgarian National plan for rare diseases (2009 – 2013); definition, codification and inventorying of rare diseases; research on rare diseases;

⁵⁶ Information extracted from the Orphanet database in May 2011.

⁵⁷ <http://www.raredis.org/>

⁵⁸ <http://bapes.raredis.org/>

⁵⁹ http://raredis.org/pub/RD_Report_01112010_EN.pdf

centres of expertise, reference networks and access to orphan drugs; patient empowerment. The analysis offered is based on three main documents – EU Council recommendation on action in the field of rare diseases, EUROPLAN recommendations and the Bulgarian National plan for rare diseases. The comments and suggestions, which came from the participants of the EUROPLAN Bulgarian National Conference for Rare Diseases, have been had in mind when completing the explored indicators.

ICRDOD also prepared in June 2010 (and updated in March 2011) a review of the access to orphan drugs for rare diseases in Bulgaria⁶⁰: the report contains 4 sections: orphan drug 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 drugs 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.

ICRDOD has also produced two FAQ documents in 2010: a “FAQ on Personalised Healthcare⁶¹” and a “FAQ on Clinical Trials⁶²” both prepared by the European Genetic Alliances Network (EGAN)⁶³ and translated in Bulgarian by the ICRDOD team. A new section was added to the ICRDOD site where users can find useful information about rare diseases and web-database links⁶⁴: the version in Bulgarian language contains also rare diseases description, prepared by ICRDOD consultants. These documents include common synonyms, definition, aetiology, clinical aspects, genetic counselling, medical treatment, specialised clinics and patient associations in Bulgaria.

In 2010 ICRDOD also presented a book entitled "On Yesterday, Today and Tomorrow⁶⁵" containing the stories of 9 Bulgarian patients with rare diseases and their families.

In December 2010 ICRDOD also started publishing a newsletter⁶⁶ on bi-monthly basis. It contains information about recent and upcoming rare diseases activities and events, interviews with patients and medical professionals, analysis and rare diseases library. 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.

Other sources of information

No specific information reported.

Best practice clinical guidelines

Several national best practice guidelines are available in Bulgaria, including guidelines prepared, adopted and published by the Bulgarian Cancer Society for oncological diseases, including rare tumors. The guidelines are actively discussed and presented during the meetings of the society and are published in its journal (ISSN 1312-6601).

Training and education initiatives

In September 2010 a training session was organised with neonatologists about the diagnosis and the treatment of lysosomal diseases.

European national conference

In 2010, ICRDOD launched an annual national conference on rare diseases. The First National Conference for Rare Diseases in Bulgaria⁶⁷ was organised within the scope of the Europlan project and took place in Plovdiv from 28 to 30 May 2010. Over 350 participants (medical professionals, representatives of government,

⁶⁰ <http://raredis.org/pub/OD%20Report%202072010%20EN.pdf>

⁶¹ <http://www.biomedinvo4all.com/biomedinvo4all/media/upload/pages/file/PersonalisedHealthcareFAQ.pdf>

⁶² <http://www.biomedinvo4all.com/biomedinvo4all/media/upload/pages/file/FAQ%20on%20Clinical%20Trials.pdf>

⁶³ <http://www.egan.eu/>

⁶⁴ <http://www.raredis.org/modules/sections/index.php?op=viewarticle&artid=112>

⁶⁵ http://raredis.org/pub/za_vcera_dnes_i_utre.pdf

⁶⁶ <http://raredis.org/modules/sections/index.php?op=viewarticle&artid=214>

⁶⁷ <http://www.conf2010.raredis.org/>

patients, medical students, representatives of Industry) attended this conference which was organised by NAPRD and BAPES. During the conference a total of 2 panel sessions, 9 workshops and 4 patient seminars was held, in which participants had the opportunity to learn best European practices and recommendations in the field of rare diseases, the priorities and objectives of the Bulgarian National Plan for rare diseases and most importantly to discuss these issues, to express their proposals in order to implement in an optimal way the policies and strategies for rare diseases in Bulgaria. 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 consultation⁶⁸.

National rare disease events in 2010

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

Rare Disease Day 2010 was coordinated by the National Alliance of People with Rare diseases (NAPRD) which represents over 25 RD patient organisations in Bulgaria. The event's patron was the Bulgarian First Lady Mrs. Zorka Parvanova. On 25 February 2010, NAPRD invited stakeholders (including representatives of national authorities, medical specialists, patient organisations, patients and pharmaceutical company representatives) to a press conference in Sofia. Held one year after the start of the Bulgarian National Plan for Rare Diseases, the preliminary results of the Plan were presented. The NAPRD presented the rare diseases agenda for 2010, including the European Conference for Rare Diseases (13-15 May 2010), the 5th Eastern European Conference for Rare Diseases (1-3 July 2010) and awareness- raising RD workshops.

On the 28th of February 2010, various awareness-raising activities took place in the towns of Sofia, Plovdiv, Varna, Burga, Stara Zagora, Pleven and Sliven as part of Rare Disease Day. NAPRD and rare disease patient organisations were involved with events such as marches, exhibitions, workshops for children and patient advocacy workshops. The day came to a close with a charity concert at Plovdiv's National Army Hall.

On the 1st of March 2010, a Rare Disease Information Day initiated by DEBRA Bulgaria and its secretary Dr. Ivelina Yordanova was held at the Pleven Medical University Campus for medical students.

On the occasion of the First School Day (15 September 2010) patient associations from the NAPRD organised a march under the motto "For a fair chance to our children" in Plovdiv. The initiative aims to draw again the attention of the society and to provoke actions from the state in order to eliminate the discrimination on rare diseases patients' medical treatment. Anyone may express its solidarity and support to the people with rare diseases by joining the rally. Following the march, patient organisations from the National Alliance of People with Rare Diseases sent a letter⁶⁹ to the Bulgarian Prime Minister Mr. Boyko Borisov. They requested a meeting with him in order to present the problems of people with rare diseases and their families and to look together for ways to solve them.

The Organisation of Thalassaemia Patients in Bulgaria organised for a second consecutive year a seminar for patients. It was held as a satellite meeting during the Europlan National conference in Plovdiv in May 2010. Around one hundred patients were made familiar with the recent developments on chelation therapy in Bulgaria, as well as blood donation initiatives and access to specialised social services for patients with Thalassaemia. Prominent lecturers from Italy and Greece, as well as representative from TIF were also present.

The Bulgarian Cystic Fibrosis Patient Association with the support of the European CF organisation and the ICRDOD, organised the First Training Workshop for Cystic Fibrosis on 29 May 2010 in Plovdiv. The aim was to present the latest developments in European standards of treatment, therapy, physiotherapy and care of patients with cystic fibrosis. The seminar highlighted training in physiotherapy, which is an integral part of overall therapy. The lecturers were medical professionals from Europe as well as medics from Bulgaria, who have experience with the treatment of patients with cystic fibrosis. The event was held as a parallel workshop

⁶⁸ [http://download.eurodis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/FINAL%20Report_Bulgarian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf](http://download.eurodis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Bulgarian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf)

⁶⁹ <http://raredis.org/pub/Open%20letter.pdf>

of the Europlan National Conference on Rare Diseases. Other patient training sessions also took place at the Europlan conference.

A large-scale rare diseases charity campaign was put in action in October 2010. A "Rare Diseases Solidarity Stand" was organised during the 16th Italian Festival of Beauty and Style. Many famous Bulgarian artists and VIPs came to support the initiative, as well authorities and representatives of local and international business in Plovdiv. The wide media coverage has really helped to increase the general awareness about this problem.

Other rare disease meetings included the 9th National Conference on Clinical Haematology (28-30 October 2010, Plovdiv); the 1st National Congress of Medical Rehabilitation and Occupational Therapy (4-6 November 2010, Borovets).

Hosted rare disease events in 2010

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 the Fifth Eastern European Conference for Rare Diseases and Orphan Drugs was hosted and co-organised in Saint Petersburg, Russia in conjunction with the first All-Russian Conference for Rare Diseases and Rarely Used Medical Technologies.

Research activities and E-Rare partnership

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. The possibility of establishing a public-private fund for rare disease research is being explored following discussions at the National Conference on Rare Diseases (28-30 May 2010) which concluded that there is a lack of rare disease research in Bulgaria at the current moment.

E-Rare

Bulgaria is not currently a partner of E-Rare.

Participation in European projects

Bulgaria participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne and Care-NMD. Bulgaria participates, or has participated, in European rare disease research projects, including: EUROGLYCANET. Bulgaria contributes to the following European registries: EUROCARE CF and TREAT-NMD. Bulgaria contributes to the EUROPLAN project.

Discussions at the National Conference on Rare Diseases (28-30 May 2010) highlighted the need to make European rare disease research projects and topics better known amongst researchers and academics in order to set up partnerships.

Orphan drugs

In June 2010, the ICRDOD also prepared a review of the access to medicines for rare diseases in Bulgaria⁷⁰, which was expanded and updated in March 2011⁷¹. The report contains information on important orphan drugs' activities and explained how they are set up in Bulgaria in 4 sections: orphan drug designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; conclusions.

Orphan drug committee

There is currently no orphan drugs specialised committee in Bulgaria. Orphan drugs are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. Both Commissions are formed by the Council of Ministers upon proposals by the Ministry of Health (MoH). From 2011, orphan drugs will be split into two groups: the first group reimbursed by the Ministry of Health, the second one by the National Health Insurance Fund (NHIF).

⁷⁰ <http://raredis.org/pub/OD%20Report%2022072010%20EN.pdf>

⁷¹ http://raredis.org/pub/OD_Report_04042011_EN.pdf

Orphan drug incentives

No specific activity reported.

Orphan drug availability

No specific information was provided on the number of orphan drugs marketed (“available”) in Bulgaria currently, however information was provided on the accessibility of orphan drugs.

Currently in Bulgaria, 22 orphan drugs (of 61 with EMA market authorisation) are priced and included in the Positive Drug List (PDL).

The remaining orphan drugs, registered by EMA, are virtually inaccessible for patients with rare diseases in Bulgaria given the fact that are outside the PDL, they are not subject to reimbursement from public funds. The average time period between a drug receiving European marketing authorisation to its inclusion in PDL is around 43 ± 29.1 months. This is mostly not due to the requirements of the Commission on PDL, but rather because of the reluctance of the producers to register the price of their medicines in Bulgaria.

Until the end of 2010, Orphan drugs in Bulgaria were available through one mechanism with steps: 1) inclusion at the Positive reimbursement drug list (appendix 3 and 4 of this list gives a list of drugs for rare diseases that should be 100% reimbursed by public resources); 2) Ordinance (MoH) 34 for expensive treatments: it defines a list of rare diseases, drugs and places for diagnosis and treatment. Several pharmaceutical companies donate orphan drugs on a volunteer basis in the country.

The drugs available in 2010 on the PDL and included in Ordinance 34⁷² are: Atriance, Elaprase, Exjade, Fabrazyme, Glivec, Litak, Nexavar, Somavert, Sprycel, Tasigna, Torisel, and Ventavis. The drugs available in 2010 on the PDL and which are not included in Regulation 34 are: Aldurazyme, Myozyme, Naglazyme, Nplate, Revatio, and Tracleer.

Starting from 2011, the reimbursement of the orphan drugs with public funds will be provided via two mechanisms:

- through Ordinance (Ministry of Health) 34 of 25 November 2005 on the procedure for payment from the state budget of the medical treatment of Bulgarian citizens, outside the scope of mandatory health insurance (through the Ministry of Health budget)
- or through Ordinance (Ministry of Health) 38 of 16 November 2004 on the list of conditions for which home treatment NHIF fully or partly pays the medicines, medical devices and dietary foods with special medical purposes (through NHIF budget).

Currently, 16 orphan drugs (from the 22 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 fact that an orphan drug is included in the PDL and reimbursed under one of the two regulations, does not mean that in practice it is accessible and available in adequate quantities for each patient. Institutions for planning and funding for treatment and rehabilitation of patients with rare diseases 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 drug reimbursement policy

There is no specific orphan drug reimbursement policy and orphan drugs are subject to the general conditions as any other medicaments.

Having been priced, orphan drugs 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. The Council of Ministers upon proposal by the Minister of Health has determined in an ordinance the conditions, rules and criteria for inclusion, amendments and/or exclusion of drugs from PDL and the terms and conditions of work of the Commission on PDL. Under this ordinance, drugs that are candidates for inclusion, should meet the following specifications: authorisation for use under MPHMA; price upon Art. 258, par. 1 of MPHMA; indication for treatment, prevention or diagnosis of diseases in accordance with Art. 2, par. 2 of the regulation itself; international non-proprietary name, to which the medicinal product belongs, is reimbursed by public funds for the same conditions or indications in at least three of the following countries: Romania, Czech Republic, Estonia, Greece, Hungary, Lithuania, Portugal and Spain; dosage mode and route of administration, which are suitable for treatment of those diseases; assessment of therapeutic value and social significance.

The Positive Drug List 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 MTFA and by the budget of the hospitals with state and/or municipal stake upon Art. 9 and 10 of MTFA;

⁷² Information taken from the report: <http://raredis.org/pub/OD%20Report%2022072010%20EN.pdf>

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 drugs 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 drugs

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

Orphan drug pricing policy

There is no specific orphan drug pricing policy and orphan drugs are subject to the general conditions as any other medicaments.

The pricing (negotiation of price and level of reimbursement) of orphan drugs in Bulgaria is determined by the Ordinance on the conditions, rules and procedures for regulating and registering the prices of medicines. The fundamental principle is that of the lowest reference values. The price of the medicinal product (which will be included in the Positive Drug List and will be reimbursed by public funds, as that is the case of orphan drugs) is formed on the basis of producer's price, which could not be higher than the lowest price for the same product, paid by public health insurance funds in Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal and Spain. Where there is no producer's price in these countries, the price is formed in the same manner and based on the following additional reference countries – Belgium, Czech Republic, Poland, Latvia and Hungary. Fixed margins for wholesalers and retailers, as well as value added tax are added to form the final price.

Orphan devices

No information reported.

Specialised social services

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

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

1.4. CYPRUS

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

There is currently no national plan or strategy for rare diseases in Cyprus, though steps are being made to establish a National Committee for Rare Diseases and prepare a national strategy. The Minister of Health of the Republic of Cyprus, Christos Patsalides announced on 28 February 2009 that in order to coordinate the best

possible existing services for treating rare diseases, and to develop research activities, the Ministry would establish a National Committee for Rare Diseases and apply a strategic plan for rare diseases. The National Steering Committee has since been established and a draft national plan for rare diseases has been elaborated. The committee is also responsible for key activities such as establishing a registry of rare diseases in Cyprus, the organisation of preventive programmes and the upgrading and expansion of centres for diagnosis, therapy and treatment. The plan will also include the development of research activities (in collaboration with the pharmaceutical industry) in efforts to offer greater support to patients and their families. A preparative workshop to exchange opinions among stakeholders is planned in early 2011 and further meetings will be arranged for the discussion of the plan with stakeholders. The Ministry of Health is also planning a conference on rare diseases in 2012, during Cyprus' EU Presidency.

Centres of expertise

There are currently no official designated centres of expertise for rare diseases in Cyprus as there are no criteria determined yet. However, the Cyprus Institute of Neurology and Genetics operates as a centre of research, treatment and management for various neurological and genetic conditions. The Clinical Genetics Clinic, located both at the Cyprus Institute of Neurology and Genetics and Archbishop Makarios III Hospital, is involved in the management of over 2500 patients and their families living with or at risk of a genetic condition in Cyprus. The Archbishop Makarios III Hospital in Nicosia is the main referral hospital for children and adolescents where most young patients with rare diseases are referred for diagnosis and management. The Cyprus Thalassaemia Centre is the main centre for screening (premarital), counselling and management of thalassaemia on the island. Several other departments and specialised clinics serve as referral centres for disorders such as rare haematological, congenital heart disorders, cardiomyopathies, etc.

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 of phenylketonuria and congenital hypothyroidism. Also a nationwide screening for congenital hearing deficit exists.

Genetic testing

Genetic testing is available for several genetic disorders. This includes conventional and molecular cytogenetics, metabolic disorders, neurogenetics, heritable cancers as well as testing for predisposing genes, thalassaemia molecular diagnostics, other blood genetic disorders and many others.

Diagnostic tests are registered as available in Cyprus for 44 genes and an estimated 55 diseases in the Orphanet database⁷³.

National alliances of patient organisations and patient representation

In June 2010, the Cyprus Alliance for Rare Disorders (CARD)⁷⁴ 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 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. A press conference was held on 23 September 2010 to launch CARD. Now legally registered, the Cyprus Rare Disease Alliance will become Cyprus' national representative for patients in health organisations and institutions at European and international level. Furthermore several other patient organisations covering exist representing (but not exclusively) rare disease patients with a disability such as vision deficit or hearing loss, patients with mental retardation, patients with Down syndrome, patients with congenital heart disorders, etc.

⁷³ Information extracted from the Orphanet database in May 2011.

⁷⁴ http://www.thalassaemia.org.cy/cyprus_alliance.html

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 II 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.

Official information centre for rare diseases

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

Help line

There is currently no rare disease help line in Cyprus.

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 Cyprus⁷⁵, 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 new website www.genenet.org.cy which provides links to Orphanet. Furthermore, the Thalassaemia National Centre is the source of information for Haemoglobinopathies. Several specialised clinics and organisations are functioning as sources of information for specific disorders.

Best practice clinical guidelines

Internationally accepted best clinical practice guidelines are 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 in the paediatric department of the Makarios Hospital and the Cyprus Institute of Neurology and Genetics, and also 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. The Cyprus Institute of Neurology and Genetics serves also as a satellite centre to the EGF courses which include several activities on rare genetic disorders.

Europlan national conference

Cyprus did not hold a Europlan national conference in 2010.

National rare disease events in 2010

National Rare Disease Day February 2010 was celebrated with a press conference by the Ministry of Health and the Cyprus Society of Human Genetics with many stakeholders invited. Several radio and television programmes took place in the weeks before and after but also through the year while numerous articles were edited in newspapers, magazines and local scientific journals and newsletters.

The 2nd International Conference of the Cyprus Society of Human Genetics in November 2010 was mainly devoted to rare genetic disorders including new therapeutic approaches for lysosomal and neuromuscular disorders.

Hosted rare disease events in 2010

Several conferences were organised during which several rare diseases were addressed.

Research activities and E-Rare partnership

Research activities

Funding opportunities for rare disease research are offered by the Cyprus Research Promotion Foundation and the Cyprus Institute of Neurology and Genetics. The Telethon is an international charitable institution which is organised by the Cyprus Institute of Neurology and Genetics (CING) to support scientific research into gene

⁷⁵ <http://www.genenet.org.cy/>

therapy for neuromuscular diseases. A large proportion of net revenue from the Telethon is allocated to the (approximately 30%) 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.

In Cyprus, preparation on the approval of clinical trials with the use of lentivirus vectors for the gene therapy of B-Thalassemia is underway.

E-Rare

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

Participation in European projects

Cyprus participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA and TAG. Cyprus participates, or has participated, in European rare disease research projects including: EUROPEAN LEUKEMIA NET, Ithamet, LEISHMED and MYELINET. Cyprus contributes to the following European registry: EUROCARE CF. Cyprus contributes to the EUROPLAN project.

Orphan drugs

Orphan drug committee

No specific activity reported.

Orphan drug incentives

No specific activity reported.

Orphan drug availability

No specific information was reported on the orphan drugs marketed in Cyprus. Several orphan drugs have been requested and approved for use, i.e. for Gaucher disease patients and others.

Orphan drug reimbursement policy

No specific activity reported.

Other initiatives to improve access to orphan drugs

Reimbursement is available for the compassionate use of orphan drugs.

Orphan drug pricing policy

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

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

1.5. CZECH REPUBLIC

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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. The Czech ten-year strategy⁷⁶ 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.

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 Prague⁷⁷ in collaboration with the University Hospital of Masaryk University Brno⁷⁸ 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.

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 drugs is reimbursed in these centres and these centres manage the provision of very expensive orphan drugs. 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.

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.

Registries

The Czech Republic contributes to some European registries such as ECFS.eu for cystic fibrosis and TREAT-NMD for muscular dystrophies, European Porphyria Network (EPNET), EuroCAT for rare birth defects, as well as the SCNIR international registry. The National Registry for Cancer⁷⁹ 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 disorders⁸⁰. Neonatal screening is routinely performed for phenylketonuria, congenital adrenal hyperplasia and congenital hypothyroidism, hyperphenylalaninemia; maple syrup urine disease; glutaric aciduria type I; medium-chain acyl-CoA dehydrogenase deficiency; long-

⁷⁶ http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf

⁷⁷ www.ublg.lf2.cuni.cz

⁷⁸ www.fnbrno.cz

⁷⁹ <http://www.linkos.cz/odbornici/onkologie/nor.php>

⁸⁰ <http://www.novorozenecky-screening.cz/>

chain 3-hydroxyacyl-CoA dehydrogenase deficiency; carnitine palmitoyl transferase 1 deficiency; carnitine palmitoyl transferase 2 deficiency; and carnitine acylcarnitine translocase deficiency and cystic fibrosis since. 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 Company⁸¹ from 2010.

Genetic testing

In terms of diagnostic services, there are over 63 molecular laboratories in the country. Together, they offer diagnostic tests for more than 531 different rare diseases⁸². Genetic counselling exists for all families at risk. Clinical genetics services are available throughout the entire country, with every major district having such services, both at private and/or state based levels. Genetic services are carried out in compliance with all international professional standards and are fully covered by the national health insurance system.

National alliances of patient organisations and patient representation

There is currently no national alliance of rare disease patient organisations in the Czech Republic. Creating an alliance for rare disease patient groups is a provision of the national strategy being developed, together with the Coalition for Health Association⁸³. However, there are 41 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.

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 School 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 an Orphanet country site in the Czech language⁸⁴.

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 website⁸⁵.

Help line

A website and a help line for rare diseases are under consideration.

Other sources of information

Patient organisation web sites are one of the few national sources of information for rare diseases in the Czech language. A web based information service on neonatal screening is available (<http://novorozenecky-screening.cz>).

Best practice clinical 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 diseases⁸⁶ and reflect EMQN.org, CMGS.org and Eurogentest.org guidelines.

Training and education initiatives

No specific activity reported.

⁸¹ www.vzp.cz

⁸² This information provided by <http://www.uhkt.cz/nrl/db/index.html?lang=en>

⁸³ www.koaliceprozdravi.cz

⁸⁴ <http://www.orphanet.cz/national/CZ-CS/index/%C3%BAvod/>

⁸⁵ The site www.vzacnenemoci.cz is under construction.

⁸⁶ <http://www.uhkt.cz/nrl/nrl-dna/blp>

Europlan national conference

No Europlan national conference took place in the Czech Republic in 2010.

National rare disease events in 2010

In order to promote the Czech National Strategy for Rare Diseases, the Czech radio station Classic FM featured a series of interviews with rare disease experts and patients which were co-financed by the Ministry of Health.

Hosted rare disease events in 2010

Amongst the rare disease events hosted by the Czech Republic in 2010 and announced in OrphaNews Europe was: the 11th EPPOSI workshop on rare disease therapy development workshop (29-30 November 2010, Prague, Czech Republic).

Research activities and E-Rare partnership

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 15 different research projects in the field of rare diseases are registered with Orphanet, focusing on 30 different rare disorders. At least three projects are targeting specific genes.

E-Rare

The Czech Republic is not currently a partner of the E-Rare research programme on rare diseases. However negotiations, with E-Rare2 project are underway.

Participation in European projects

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. Teams in the Czech Republic participate, or have participated, in the European rare disease research projects, including: CLINIGENE, ENCE PLAN, EUMITOCOMBAT, EURO-PADNET, EUROCARE-CF, EUROPEAN LEUKEMIA NET, EUROAGENTEST, EUROGLYCANET, 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: EUROCARE CF, EUROCAT and TREAT-NMD. The Czech Republic is also a partner country of the Severe Chronic Neutropenia International Registry (SCNIR), monitoring the clinical course, treatment, and disease outcomes in patients with severe chronic neutropenia.

The Czech Republic also participates in many international-level activities including ERNDIM (a consortium for quality assessment in biochemical genetics for rare disease) and Europlan, developing guidelines for national rare disease plans.

Orphan drugs

SUKL⁸⁷, 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 drugs.

Orphan drug committee

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

Orphan drug incentives⁸⁸

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 drug 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

⁸⁷ www.sukl.cz

⁸⁸ 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)

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

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

“Under §26d(1) of Act No 79/1997 Coll. On medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may, in the case of orphan medicinal products in justified cases meeting the conditions laid down by decree, allow the registration of a medicinal product or the placing on the market of individual batches of a medicinal product even where the data are indicated on the packaging in a language other than Czech.⁸⁹”

Orphan drug availability

In May 2010, 62 orphan drugs were registered in the Czech Republic of which 28 are were distributed on a centre basis and are completely reimbursed. The orphan drugs registered in the Czech Republic are: Afinitor, Aldurazyme, Arcalyst, Arzerra, Busilvex, Carbagli, Cyaston, Ceplene, Cystadane, Diacomit, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyf, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Peyona, Photobarr, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Siklos, Soliris, Somavert, Tasigna, Tepadina, Thalidomide Celgene, Thalidomide Pharmion, Thromboreductin, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Vpriv, Wimzin, Xagrid, Xyrem, Yondelis, Zavesca.

Orphan drug reimbursement policy

Not all orphan drugs are reimbursed; those which are distributed on a centre basis (see section on “Orphan drugs availability”) are completely reimbursed. In 2008 a cap to the co-payment by patients of 5000 CZK (€187) per year was established for prescription medicines.

Other initiatives to improve access to orphan drugs

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

Orphan drug pricing policy

No information reported as yet.

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.

⁸⁹ *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 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, though Rare Diseases Denmark is lobbying for a plan. 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 Diseases in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark (see section "Europlan national conference").

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 established referral centres/centres of expertise approved by the National Board of Health to maintain a specific or several specific rare diseases⁹⁰.

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 programmes, 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

⁹⁰ 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/RDTFECR2006.pdf>

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 a nominated centre.

According to the Danish Health Care Act from 2007 the National Board of Health began a comprehensive work going through the organisation of specialised diagnoses, treatments and medical technologies across 36 surgical, medical and diagnostic specialities. The main goal was to improve quality through sufficient volumes of patients and experienced professionals. The general criteria for establishing centers of expertise in this context are rareness, complexity, multidisciplinary and costly technologies. In 2009 public and private hospitals could apply to the National Board of Health for approval to maintain specific specialised treatments. In 2010 the National Board of Health announced the approved hospital departments.

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 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 specialised 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.

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 special 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 departments. 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 134 genes and an estimated 204 diseases in the Orphanet database⁹¹.

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

⁹¹ Information extracted from the Orphanet database (May 2011).

clinical data. The hereby collected information can be used for research projects and bench marking at a Nordic level for different rare diseases.

Denmark contributes to some European registries such as EURO CARE CF, EMHG and EURO CAT.

National alliances of patient organisations and patient representation

Rare Disorders Denmark, founded in 1985, is the national alliance of 42 rare disease patient organisations. 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. Rare Disorders Denmark has developed a tool, Social Profiles, to promote dialogue between rare disease patients and professionals. The profiles are currently available for 22 rare diagnoses, with more to come. The profiles are published on the "Rare Citizen" website www.sjaeldenborger.dk. Rare Disorders Denmark marked its 25th anniversary in 2010. The alliance organised a number of activities to mark Rare Disease Day in 2010 (see section "National Rare Disease Events") and was the organiser of the Europlan National Conference on Rare Diseases. Rare Disorders Denmark is also currently engaged in dialogue with the Ministry of Social Affairs (see section "Sources of information") concerning the future of the provision of information on rare diseases. A government funded 3-year project "Rare Family Days – empowerment and networking for rare families" starting in 2009 is aimed at creating a concept for patient education in the field of rare diseases. The primary target groups are families with diagnoses so rare they do not have a relevant patient association to join. The project is led by Rare Disorders Denmark

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 (Videnscenter for Handicap og Socialpsykiatri).

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*⁹²) has been functioning since 1990 with a public database containing short descriptions in Danish on rare diseases. The centre provided information, as well as guidance, especially on social issues, and provided contact with patient organisations. The CSH also ran a rare disease help line which provided information and support. The CSH maintained a database of approximately 400 rare disease patients who are currently without patient organisation representation for their disease. The CSH also contributed to Rarelink.eu, the Nordic website compiling links relating to information on rare diseases.

At the end of 2010, the Ministry for social affairs closed the Centre for Rare Diseases and Disabilities (*Center for Små Handicapgrupper* – CSH) as an independent institution. This decision was a consequence of the merger of 3 information and knowledge networks and 13 research centres in areas overseen by the Ministry of Social Affairs to form a new Centre for Disability and Social Psychiatry (*Videnscenter for Handicap og Socialpsykiatri* - ViHS⁹³) 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 meeting established the need to consider the changing landscape of RD in Denmark and the roles of various stakeholders. CSH has ensured its users that the same services will be offered as before the merger.

⁹² www.csh.dk

⁹³ 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)

Help line

Up till 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.

Other sources of information

No specific activity reported.

Best practice clinical 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. Futhermore, they provide teaching of other health care professionals, families, teachers and caretakers.

Europlan national conference

On 19 November 2010, Rare Disorders Denmark in collaboration with Eurordis held a National Conference on Rare Diseases in the context of the Europlan project. Rare disease patient associations, policy makers, researchers, social and health care professionals and the pharmaceutical industry met for the conference at Rigshospitalet in Copenhagen. The day was organised by Rare Disorders Denmark in collaboration with a steering committee with participation from medical professionals and the National Board of Health, and was intended to pave the way for a Danish strategy for rare diseases and disabilities. During the day a number of areas were tackled: The state of organisation and achievements of rare diseases regarding diagnoses, treatment, orphan drugs, coordination of healthcare for individual patients, multidisciplinary health care, the capacity of specialised centres to treat rare disease patients, the transition from childhood to adulthood, and the development of both national and international networks. Also discussed was a proposal for a centralised rare disease registry and the strengthening of national and international registry and database cooperation. Concerning research, it was agreed that there should be a sharper focus on the perspectives of research on rare diseases by implementing strategic research or a dedicated research program. Focus was centred on the need to strengthen the position of patients and patient organisations in Denmark. In conclusion, Rare Disorders Denmark requested a meeting with the Minister of Health to hear more on plans for elaborating a national strategy for rare diseases in Denmark. The final report is available online.⁹⁴

National rare disease events in 2010

Rare Disorders Denmark organised a number of activities to mark Rare Disease Day in 2010. The alliance hosted two POLKA Play-Decide game nights where participants were invited to reflect actively on topics such as orphan drugs and neonatal screening and discuss various policy scenarios. On 26 February 2010 a mini round table with representatives from pharmaceutical companies and the member organisations of Rare Disorders Denmark was held. On 28 February 2010 Rare Disorders Denmark hosted a conference on genetics and human reproduction where various experts discussed the ethical and bio-technology aspects of genetic selection. On 4 March 2010, members of parliament met members of the Rare Diseases Executive Committee to discuss topics concerning neonatal screening.

Hosted rare disease events

In 2010 the following rare disease events were announced in *OrphaNews Europe*: European Conference on Post Polio Syndrome (31 August – 02 September 2011, Copenhagen).

Research activities and E-Rare partnership

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.

⁹⁴[http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report denmark_europlan.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_denmark_europlan.pdf)

E-Rare

Denmark is not currently an E-Rare partner.

Participation in European projects

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. Danish teams participate, or have participated, in a number of European research projects for rare diseases, including: ALPHA-MAN, CILMALVAC, EURHAVAC, E-IMD, 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. Amongst others, Danish teams contribute to the following European registries: EUROCARE CF, EMHG and EUROCAT. Denmark contributes to the EUROPLAN project and EU Network of experts on newborn screening.

Orphan drugs**Orphan drug committee**

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

Orphan drug incentives

Upon request, the Danish Medicines Agency may provide free scientific advice in the development of Orphan Drugs⁹⁵.

Orphan drug availability

Out of the 59 drugs with an EU market authorisation (of these 8 have 2 or more indications), 51 are approved in Denmark. The approval process usually takes 6-8 weeks.

The list of orphan drugs approved in Denmark includes: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Cystadane, Diacomit, Elaprased, Evoltra, Exjade, Fabrazyme, Firazyr, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Torisel, Tracleer, Ventavis, Vidaza, Volibris, VPRIV, Wilzin, Xagrid, Yondelis, Zavesca.

Orphan drug reimbursement policy

There is no reimbursement policy that pertains specifically to orphan drugs. In many cases, orphan drugs are restricted to hospitals.

Other initiatives to improve access to orphan drugs

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)*⁹⁶.

Orphan drug pricing policy

Manufacturers and importers of pharmaceutical products are free to set the price of each pharmaceutical. However, orphan drugs 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 devices

No specific activity reported.

⁹⁵ 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)

⁹⁶ 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 (pp 10)

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 European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

There is currently no plan for rare diseases in Estonia and there no preparations for a rare disease plan are currently underway. Rare disease costs are currently included within the general health system budget as there are no specific funds dedicated to rare diseases.

Centres of expertise

There are currently two clinical genetics centres specialising in the diagnosis and treatment of rare diseases in Estonia, Tartu University Hospital and Tallinn Children's Hospital.

Registries

There is currently no national rare diseases registry in Estonia. Estonia participates in the EURO CARE CF European registry.

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 hospital in Estonia: Children's Clinic of Tartu University Hospital or Tallinn Children's Hospital. Both hospitals have medical genetics services for early detection and prevention⁹⁷. Early detection or treatment of rare diseases is provided using DNA diagnostics and neonatal screening programmes are in place for phenylketonuria, congenital hypothyroidism and Duchenne and Becker muscular dystrophy since 1995.

Genetic testing

Genetic testing for 28 different diseases is currently available at the Centre of Genetics at Tartu University Hospital⁹⁸. Diagnostic tests are registered as available in Estonia for 160 genes and an estimated 78 diseases in the Orphanet database⁹⁹.

National alliances of patient organisations and patient representation

There is currently no national alliance for rare disease patient organisations in Estonia. Support for patients' associations comes from a national budget for *Eesti Patsientide Esindusühing* (Estonian Patients' Associations). In addition there are plans to use funds from the gambling tax for project-based financing of patients' associations.

Patient organisations are represented on the council of the Estonian Health Insurance Fund and grants are available for patient organisations to attend these meetings.

⁹⁷ <http://www.kliinikum.ee/geneetikakeskus/>

⁹⁸ See the regularly updated list in Estonian for further information: <http://www.kliinikum.ee/geneetikakeskus/>

⁹⁹ Information extracted from the Orphanet database (May 2011).

Sources of information on rare diseases and national help lines

Orphanet activities in Estonia

Since 2004, there is a dedicated Orphanet team in Estonia, currently hosted by the Estonian Biocentre. The team was designated as 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.

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.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

There are special advanced courses for physicians (2-3 courses per year) on rare disorders, aimed at improving the early detection and diagnosis of certain rare diseases (Prader-Willi syndrome, Angelmann syndrome, SMA, Dravet Syndrome, etc). In 2009 the number of advanced courses on rare disorders organised by the Department of Continuing Education at the Tartu Medical University increased, due to rising interest in the subject. Additional courses took place in 2010.

Europlan national conference

Estonia did not hold a Europlan national conference in 2010.

National rare disease events in 2010

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.

To mark Rare Disease Day two articles¹⁰⁰ appeared on 1 March, 2010 in two Estonian national newspapers: *Postimees* and *Õhtuleht*. The articles talked about Rare Disease Day, drugs for rare disease and the need for specific policies targeting rare diseases in Estonia. The articles also presented an overview of the definition of a "rare disease", gave an idea of the number of RD patients in Estonia, and highlighted the main concerns regarding treatment in the field.

Hosted rare disease events in 2010

No specific activity reported.

Research activities and E-Rare partnership

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 600-800'000 EEK available over four years)¹⁰¹. Some projects that involve research on rare diseases are financed by Targeted Financing from the Estonian Government (congenital adrenal hyperplasia, phenylketonuria, Prader-Willi syndrome).

¹⁰⁰ Postimees: <http://www.tarbija24.ee/?id=230871>

Õhtuleht: <http://w3.ee/openarticle.php?id=1159224&lang=est>

¹⁰¹ 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)

E-Rare

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

Participation in European projects

Estonian teams participated, in the following European Reference Network for rare diseases: PAAIR. Estonian teams participate, or participated, in European rare disease research projects, including: AAVEYE, EURAPS, MOLDIAG-PACA and RD PLATFORM. Estonian teams contribute to the following European registries: EUROCARE CF. Estonia contributes to the EUROPLAN project.

Orphan drugs***Orphan drug committee***

There is currently no orphan drug committee in Estonia.

Orphan drug incentives

There are no specific incentives for orphan drugs in Estonia.

Orphan drug availability

In theory, all orphan drugs with EU market authorisation can be bought in Estonia, but due to the high cost of these drugs, only those which are reimbursed by *Eesti Haigekassa* (Estonian Health Insurance Fund) are easily accessible. Patients can access all other orphan drugs if they are willing to pay the cost of the drug.

Orphan drug 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, its chronic nature 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. Currently¹⁰² *Haigekassa* reimburses patients 100% of the costs of 9 orphan drugs: Fabrazyme, Replagal, Tracleer, Glivec, Revatio, Nexavar, Sprycel, Sutent, Wilzin.

Other initiatives to improve access to orphan drugs

There are no specific programmes to facilitate the provision of medicines to rare disease patients.

Orphan drug pricing policy

There is no specific pricing policy for orphan drugs in Estonia.

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 Foundation 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 2010, several respite camps were organised 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

¹⁰² Information accurate in May 2011.

are provided by patient organisations and are partially reimbursed. Services exist to promote the integration of patients with disabilities in schools and in the work place and are financed by the government.

1.8. FINLAND

Definition of a rare disease

There is no official definition for rare diseases in Finland. The definition in most Nordic countries of a rare disease is a disease with a prevalence of no more than 100 people per 1,000,000 inhabitants. This definition has been used for practical purposes. At present the parties involved in the field of rare diseases are gradually introducing the common EU definition: in matters concerning orphan drugs Finland already applies the Orphan Drug regulation definition of no more than 5 in 10'000 individuals in the EU.

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. Discussion between the Finnish Ministry of Social Affairs and Health, the National Institute for Health and Welfare and the Harvinaiset Network for Rare Diseases about co-operation in this matter are under way. 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) to publish a report concerning cooperation possibilities between Nordic countries in the field of rare diseases. The project is supported by the Nordic Council of Ministers, and is 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 conclusion¹⁰³ 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 paediatric 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).

Registries

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. Finland contributes to European registries including TREAT-NMD and EUROCAT.

Neonatal screening policy

All newborns are screened for hypothyroidism. There is an ongoing pilot scheme of screening additional five metabolic diseases congenital adrenal hyperplasia (CAH), MCAD deficiency, LCHAD deficiency, Glutaricaciduria type 1 (GA1), and phenylketonuria in the Turku area, concerning around 3000 newborns per year. No decision has yet been made concerning the widening of the neonatal screening programme. In addition to this, paediatricians organise screening for phenylketonuria in newborns of non-Finnish origin.

¹⁰³ <http://www.nordicwelfare.org/filearchive/1/119089/Rapport%20med%20bilagor%20final.pdf>

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) consent is always sought for medical tests. 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 162 genes and an estimated 207 diseases in the Orphanet database¹⁰⁴.

National alliances of patient organisations and patient representation

There is currently no organised national alliance of rare disease patient organisations in Finland. There has been recent discussion amongst patient organisations concerning the creation of a national rare disease alliance.

There is no official or unofficial body representing rare diseases patients or patient organisations in social decision making or other policy issues. 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 country site acting as a national entry point to the database.

In 2010 Orphanet and Terveysportti¹⁰⁵ established a collaboration. Terveysportti is maintained by Duodecim, the Finnish Medical Society, a scientific society adhered to by almost 90% of Finnish doctors and medical students. The Terveysportti portal is for healthcare professionals and is used nationwide in public health care units, hospitals, private practices and pharmacies as well as the universities' medical faculties. The service consists of more than 35 databases and helps professionals find day-to-day medical information quickly and reliably from one source. During 2010 links to Terveysportti's Finnish texts were added to Orphanet's disease abstract pages for more than 300 rare diseases. Orphanet is thus included in Terveysportti's searched 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.

¹⁰⁴ Information extracted from the Orphanet database (May 2011).

¹⁰⁵ <http://www.terveysportti.fi/>

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. The Harvinaiset network also participates in the maintaining of the Nordic website www.rarelink.fi.

Most providers of web-based information on diseases in general have phone or web answering services and a possibility to make on-site visits: they provide general information about diseases, contacts for treatment, advocacy, rehabilitation, psychological support and support from patient organisations or peer support groups.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

Europlan national conference

Finland did not hold a Europlan national conference in 2010.

National rare disease events in 2010

In Finland Rare Disease Day 2010 was coordinated by Harvinaiset, the Finnish Network for Rare Diseases. To mark the day an event was held in cooperation with The Finnish Science Centre Heureka on 28 February at Heureka in Vantaa. The event included PlayDecide sessions¹⁰⁶, lectures, discussions, information (including demonstrations of the Orphanet database) and activities for the whole family. The patron of the event was Minister of Health and Social Services Paula Risikko.

Harvinaiset also held a seminar¹⁰⁷ on 27 September 2010 in Helsinki on the EU Council Recommendation on an action in the field of rare diseases and the elaboration of a national plan for rare diseases in Finland.

A Rare Diseases Day for Doctors was arranged 29 October 2010 in Helsinki for the second time and there is a plan to arrange it on a yearly basis. It was organized by five Scientific Societies of Medical Specialties: (Paediatrics, Rheumatology, Hematology, Child Psychiatry, and Medical Genetics), Orphanet Finland, ORTON (Orthopaedic Hospital and Rehabilitation), PerkinElmer Finland, and Swedish Orphan Biovitrum Ab. The Minister of Health and Social Services Paula Risikko made a promise about a Finnish national plan for rare diseases in her speech. There were presentations and workshops with discussions about experiences of rare disease patients on care in Finland, research, newborn screening, and therapy in the field of rare diseases.

Hosted rare disease events in 2010

No specific information reported.

Research activities and E-Rare partnership**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 amongst more common ones, like hereditary nonpolyposis colorectal cancer (HNPCC), hereditary connective tissue diseases, and long QT syndrome, have been studied.

¹⁰⁶ <http://www.playdecide.eu/>

¹⁰⁷ <http://harvinaiset.fi/ajankohtaista/harvinaiset-verkoston-syksyn-seminaarin-antia> (accessed 28/01/11)

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.

E-Rare

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

Participation in European projects

Finnish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET and EPI. Finland participates, or has participated, in European rare disease research projects including: BNE, CLINIGENE, EUGINDAT, EUMITOCOMBAT, EURAPS, EUREGENE, EURO BONET, EURO GENTEST, EUROPEAN LEUKEMIA NET, GEN2PHEN, LYMPHANGIOGENOMICS, NEUROPRION, PEROXISOMES, PROTHETS, PULMOTENSION, TREAT-NMD and RD PLATFORM. Finland contributes to the following European registries: TREAT-NMD and EUROCAT. Finnish experts also contributed to the EUROPLAN project.

Orphan drugs

Orphan drug committee

No specific information reported.

Orphan drug incentives¹⁰⁸

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 drugs are stated in the Health Insurance Act. However, the health economic evaluation is not always required from the marketing authorisation holder of orphan drug if justified by the applicant.

Orphan drug availability

The *Fimea* website¹⁰⁹ lists the following orphan drugs as available on the market in Finland: Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyf, Gliolan, Glivec, Increlex, Inovelon, Litak, Lysodren, Mozobil, Myozyme, Nexavar, Nplate, Onsenal, Orfadin, Pedeo, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Vpriv, Xagrid, Yondelis, Zavesca.

Orphan drug 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*¹¹⁰ 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 letter¹¹¹ to the Ministry of Social Affairs and Health concerning the reimbursement of orphan drugs 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

¹⁰⁸ 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)

¹⁰⁹ <http://www.fimea.fi/medicines/fimeaweb>

¹¹⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p12)

¹¹¹ http://harvinaiset.fi/ajankohtaista/stm-n-vastaus-kannanottoon-laeakehoidon-korvauksista&rurl=translate.google.fr&twu=1&usg=ALkJrh-90epJLiXoahxcmk5V47DH0lr_Av

treatments (including orphan drugs), 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 drugs

No specific information reported.

Orphan drug 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*¹¹² 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 devices

No specific information reported.

Specialised social services

Respite care services are available and local authorities are responsible for their provision, but some are equally provided by private institutions: patients and families often have to provide co-payment. Therapeutic recreational programmes are available under different forms and patients have to partially pay for these services though some funding can be provided by RAY. Services for transport, modifications for housing arrangements, day-care, interpreter (sign language etc), personal assistants etc are available for those with handicaps by local authorities, provided for by the law 380/1987 in 1987 (updated 1267/2008 and 981/2008). Patients with a rare disease, as well as all others with a severe disability, were given new possibilities 2009. The legislation for personal assistance was updated as of 1 September 2009. This update follows the principles of Independent Living Movement. Personal assistance for persons with a severe functional disability is free of charge. Besides the support in the daily living, work and education this now also includes assistance with participation in recreational activities, social activities and education. The service is financed by the municipalities.

¹¹² *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p12)*

1.9. FRANCE

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

First French National Plan for Rare Diseases (2004-2008)

France was the first EU country to put in place a comprehensive rare disease plan (2004-2008) with allocated funding. The axes of this plan were to:

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

The first national plan provided for the official recognition and evaluation of centres of expertise (called Centres of Reference in France); new rare disease research networks and research projects are supported by a national call for proposals; information on rare diseases, orphan drugs and related fields was developed by Orphanet (established in 1997, but whose budget was increased significantly thanks to the Plan). Help lines and rare diseases identity cards were also developed. Several new information products were developed such as emergency guidelines and good practice guidelines for rare diseases (which are posted on the Orphanet website) and emergency cards to be kept by the patients in case of need.

Funding for this plan was provided within the general health system budget with ad hoc funding on the basis of rare disease projects. The funding allocated to rare disease actions is identifiable (over €100 million for the four year period).

Evaluation of the First Plan

The first National Plan for Rare Diseases underwent intense scrutiny during its five-year term which concluded at the end of 2008. The overarching goal of the evaluation of the plan was to provide data to serve for the elaboration of the second version of the rare disease plan, due in 2010. An Evaluation Committee (Codev) consisting of health, economic and sociology experts, under the authority of the French Council for Public Health, thus measured the initial objectives of the plan against the corresponding actions undertaken during the past four years. An official report of the evaluation was rendered to the French Minister of Health on 7 May 2009. The document provides an analysis of the accomplishments, advances, and shortcomings of each of the ten axes of the plan. A series of propositions and recommendations was also provided for the elaboration of the future plan.

Throughout the evaluation, the committee underscores the satisfaction of the different stakeholders vis-à-vis the overall results accomplished. The objectives judged most pertinent – the access to information (particularly Orphanet and MRIS, the French rare disease informational service helpline), medical care (centres of reference), research funding, orphan product accessibility, and partnerships with European institutions – have benefited from corresponding actions that have satisfactorily fulfilled these goals. The need to sustain these actions was reiterated in the evaluation. However, certain 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 tactics to overcome obstacles.

The tenth axis of the plan, "Develop national and European partnerships in the field of rare diseases" received an overall favourable evaluation with certain propositions presented to enhance and encourage European collaboration. Furthermore, the evaluating 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 is emphasised.

The evaluation¹¹³, along with an additional report¹¹⁴ drawn up by the Ministry of Health containing auto-evaluations from the plan's pilot committee, and the testimonies of rare disease health professional, industry and patient organisation stakeholders who contributed actions to the first plan, were discussed at the final meeting of the Follow-up Committee for the first French National Plan.

The Second French National Plan for Rare Diseases (2011-2014)

The second French National Plan for Rare Diseases¹¹⁵ was elaborated during 2009-2010 and was launched on 28 February 2011 on the occasion of Rare Disease Day with a budget of €180 million. The second plan has been streamlined to function as efficiently as possible while retaining all of the elements essential to adequately care for the country's over three million rare disease patients. The ten axes of the first plan have been consolidated into 3 main axes: improve the quality of health care for rare diseases patients, develop research on rare diseases, and increase European and international cooperation in the field of rare diseases. These axes encompass areas such as development indicators; health care coverage; information and training; organisation of care and diagnostics; targeted medicines; research; and European and international cooperation. The key measures of the plan are the creation of a Foundation for Scientific Cooperation and tools to improve the monitoring of various activities relating to rare diseases which includes the adoption of the Orphanet nomenclature and the restructuring of reference and competence centres into coherent networks.

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

A second national plan for cancers¹¹⁶ was announced on 2 November 2009 for the period 2009-2013. This plan follows a first plan¹¹⁷ 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.

Second French National Plan for Rare Handicaps (2009-2013)

A plan aimed at rare handicaps (of which rare diseases can be a cause) was adopted in 2009 for the period 2009-2013¹¹⁸. The main objectives are: the centralisation and dissemination of information on rare handicaps in collaboration with Orphanet; the consolidation, development and evolution of specialised expertise at national level; the reinforcement and organisation of the identification of rare handicaps and multidisciplinary functional evaluation across France; the creation of interregional relays; and the development of the offer of services at the homes of those with rare handicaps and in establishments. Measures include the creation of 300 additional places in care centres, regional relays, and 3 new resource centres. Cooperation between national resource centres for rare handicaps and the French "reference centres" for rare diseases is planned.

Other national initiatives related to rare diseases

On 16 May 2008, the French Health Ministry announced a national plan for 2008-2010 aimed at improving the treatment of patients with autism, improving social care for patients and their families and better educating health professionals about this rare disease.

In June 2008, the French Health Ministry announced a national plan for visual handicaps between 2008-2011 aimed at improving treatment, social care, mobility and social integration of this section of the population¹¹⁹.

On 10 February 2010, a Plan for the Deaf and Hard of Hearing was launched by the Minister for Employment, Social Affairs, Family, Solidarity and the Town, to follow up on the law of 11 February 2005: the plan has €52 million earmarked for 52 measures including: the improvement of the prevention and screening; to better accompany the deaf and hard of hearing through their life; and to make society more accessible to the deaf and hard of hearing.

¹¹³ http://www.hcsp.fr/docspdf/avisrapports/hcsp20090317_maladiesRares.pdf

¹¹⁴ http://www.sante.gouv.fr/IMG/pdf/Evaluation_interne_Plan_National_Maladies_Rares_2005-2008.pdf

¹¹⁵ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

¹¹⁶ http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf

¹¹⁷ <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

¹¹⁸ http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf

¹¹⁹ http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUN08.pdf

A system of digital, personalised medical records was launched on 16 December 2010¹²⁰ in France after a pilot test phase. This initiative will hopefully ensure a more efficient medical follow-up for rare disease patients, especially easing communication of information between the different specialists, GPs and centres of expertise involved in the health care of rare disease patients.

The *Haute Autorité de Santé* (HAS – French High Health Authority) and the *Agence de la Biomédecine* (French Biomedicine Agency) signed a collaboration on 14 December 2010¹²¹ 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. A committee to follow up on this collaboration has been created.

Centres of expertise

The National Rare Diseases Plan (2004-2008) introduced a structured organisation of health care for rare disease patients. A designation process was put into place to name centres of scientific and clinical excellence in the field of rare diseases. By the end of the plan, 131 “Reference Centres” in France were named. These centres have 6 main missions: to facilitate diagnosis and define a course of treatment; to define and publish treatment protocols in collaboration with the *Haute Autorité de Santé* (HAS) and the national health insurance bureau (CNAM); to coordinate research and participate in epidemiological surveillance in collaboration with the French Institute for Public Health Surveillance (InVS); to participate in training and information programmes for health professionals, patients and their families, in collaboration with the National Institute of Prevention and Health Education (INPES); to coordinate networks of health visitors and social workers; to be the contact point for patient organisations and social workers.

A second type of centre were designated in 2008: named “*centres de competence*” these qualified centres are identified by the reference centres and designated by Regional Hospital Agencies (ARH) whose aim is to assume responsibility for treatment and follow-up of the patient close to their home, and to participate in the entirety of the reference centres’ tasks. These qualified regional centres (“*centres de competence*”) take in charge patients from their region: 500 of these centres have been named corresponding to 1 competence centre per region in each of the large categories of centres of reference.

The reference centres are evaluated over time by the National Consultative Designation Committee (*Comité National Consultatif de Labellisation - CNCL*) first through self-evaluation after 3 years as a designated centre, with an external evaluation at 5 years. The centres have a double role: they are an expert centre for 1 or more diseases and they are a resource centre for patients referred to it.

Rare cancers had been initially excluded from the 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 (*l’Institut National du Cancer - INCA*¹²²) published a report on the advances made in structuring of the health care offer for rare cancers, which was one of the key measures of the National Cancer Plan (2009 -2013): this includes the creation of a system of national ‘reference centres’ and regional ‘competence centres’ for rare cancers. Centres have been designated as of 2009 for 15 rare cancers and four anatomopathological reference networks have been set up. These designated centres receive financial support.

There are also three designated reference centres for rare handicaps.

Registries

The National Rare Disease Registry Committee was created in October 2006 as a measure of the First National Plan for Rare Diseases with the aim of 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 giving an opinion on the suitability of the envisaged means for managing registries. Members include professionals with expertise in the field of rare diseases, public health, and representatives of users of the health system and are nominated for a 2 year term. The Committee will also participate in an annual plan to diffuse and valorise information produced by qualified registries.

In December 2008, the National Rare Disease Registry Committee designated 6 registries, as part of Axe 1 ‘Improve Knowledge of Epidemiology of Rare Diseases’ of the National Rare Diseases Plan. Three new national registries were designated in 2010 for the following rare diseases: esophageal atresia, arterial pulmonary hypertension and hereditary immune system disorders.

¹²⁰ http://esante.gouv.fr/sites/default/files/CP_OuvertureServiceDMP_141210.pdf

¹²¹ 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

¹²² <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

In December 2010¹²³ a new set of members were nominated to the National Committee for Rare Disease Registries. A second call for proposals was launched in 2010 for a new set of designations for rare disease specific registries.

It is foreseen in the second National Plan for Rare Diseases to create a national data bank containing a minimal data set to be filled in concerning patients with rare diseases in order to collect a minimum amount of common information.

The *Institut de Veille Sanitaire* has already analysed the 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 rare diseases. This work has been cited in the Second National Plan for Rare Diseases and the first results are available online¹²⁴.

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

Neonatal screening policy

A neonatal screening programme is in place in France for all newborns for the following diseases: cystic fibrosis, phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism and (for newborns presenting a risk of developing the disease) sickle cell anaemia.

In 2010, an assessment of the opportunity to extend neonatal screening to one or more inborn errors of metabolism by tandem mass spectrometry in the general French population was launched and the results are expected in 2011.

Genetic testing

The French Biomedicine Agency, a public organisation operating under the supervision of the Minister of Health, was created under the Bioethics Law of 2004. Its overriding function is to “*guarantee equity, ethics, and transparency for the activities under its responsibility and for anticipated developments*”. The 2009 annual report¹²⁵ of the French Agence de Biomédecine featured for the first time data on the post-natal genetic testing activity performed in the country. Under French law, laboratories are obliged to report their activities to the watchdog agency. The data, collected via a partnership with rare disease information portal Orphanet, were for the first time subject to an electronic analysis. Data were culled from 239 laboratories, of which 75 perform cytogenetic testing, and 182 offer molecular genetic testing. Of this latter group, laboratories offer a range of between one and 78 tests, although over 30% limit their scope to just one or two tests.

The 2009 report shows that genetic testing activity is robust in France, with over 270,000 molecular genetic analyses performed on 1042 of the 1143 genetic tests available in the country. These diagnostics concerned 951 different disorders – many of which are rare. These figures demonstrate that the molecular genetic test offer available in France must be maintained. Although just two indications – hemochromatosis and non-rare thrombophilia – represented more than 41% of analyses performed in 2009, the results illustrate that there was at least one demand for over 90% of the available tests. Other genetic tests performed in 2009 included over 6,400 pharmacogenetic analyses – a growing field of demand for genetic testing.

For cytogenetic testing, some 80,000 analyses were performed using caryotype (over 68,200) or FISH (12,000) techniques. Intellectual deficit, malformations, and developmental anomalies were amongst the indications. The new CGH array technology was used by both cytogenetic and molecular laboratories. Some 6,600 such tests were performed, most often (91% of cases) for intellectual deficit/malformations. A high level of unbalanced rearrangements was detected via this technique, probably a reflection of the fact that CGH arrays were performed in complement to a caryotype analysis.

Besides post-natal testing activity, the annual report contains the data from prenatal diagnostics undertaken in 2008, with a comparison between the years 2006, 2007, and 2008. Over 80,000 foetus were subject to cytogenetic analysis in over 70 laboratories in 2008. Of these, almost 4,000 had a positive diagnosis. Maternal age, parental chromosomal anomalies, prior pregnancies with a chromosomal anomaly, and ultrasound-detected anomalies were amongst the most frequent indication for cytogenetic testing.

Of 3,147 fetuses subject to molecular genetic testing in 2008, some 500 had positive diagnoses rendered. Cystic fibrosis, SMA, sickle cell anaemia, beta-thalassaemia, X-linked disorders, and Rett syndrome

¹²³ <http://www.legifrance.gouv.fr/affichTexte.do?dateTexte=&categorieLien=id&cidTexte=JORFTEXT000023386975&fastPos=1&fastReqId=1558215089&oldAction=rechExpMesuresNominatives>

¹²⁴ <http://www.invs.sante.fr/surveillance/index.htm> (Section “Maladies Rares”)

¹²⁵ <http://www.agence-biomedecine.fr/annexes/bilan2009/accueil.php>

were amongst the most frequent autosomal recessive conditions tested, while Steinert myotonic dystrophy, Charcot-Marie-Tooth disease, neurofibromatosis type 1 and Huntington disease were amongst the autosomal dominant conditions most frequently tested. Uniparental disomies (Prader-Willi/Angelman syndrome) were also tested in over 300 fetuses. Overall, for the molecular genetic tests, 17% of fetuses tested were affected. Between 50% and 90% of affected pregnancies were terminated, depending on the condition. Testing for these conditions was typically initiated due to an existing condition in the family or following an anomaly detected by ultrasound examination. 2009 saw the technology for pre-natal diagnostics advance, with the possibility to obtain an analysis combining nuchal translucency and a blood screen test before 12 weeks of pregnancy. For molecular genetic testing, technology now allows genotyping using the foetal DNA circulating in the maternal blood.

The annual report also includes data on cell, tissue and organ donations and transplantations, embryonic and stem cell research, and assisted reproductive activities.

Diagnostic tests are registered as available in France for 1078 genes and an estimated 1151 diseases in the Orphanet database¹²⁶.

National alliances of patient organisations and patient representation

The *Alliance Maladies Rares* (French Alliance for Rare Diseases) is the main umbrella organisation dealing with rare diseases and it plays a major role in organising working groups, communicating on rare diseases, offering support to patients and families and contributing to the development of the National Plan for Rare Diseases and the evaluation of the plan. This alliance played a role in the elaboration of the first and second national plan and the evaluation of the centres of reference. The French Rare Disease Alliance, L'Alliance Maladie Rares, 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.

The *Alliance Maladies Rares* and other patient organisations have also received some public funding during the first Plan 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 Diseases Platform (*Plateforme Maladies Rares*, established in 2001), and most particularly for the Orphanet portal on rare diseases, has been reinforced under the National Plan, 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. A new more user-friendly version of Orphanet 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 drugs 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) and is now 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 disabilities coding systems. Orphanet will introduce specific chapters on disability in the General Public encyclopedia for rare diseases which lead to handicap, whether this handicap is rare or not. Orphanet will also provide methodological support to reference centres for rare disabilities (three such centres exist today in France) in order to help them produce best 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, which will be useful to patients, families and health professionals dealing with handicaps.

¹²⁶ Information extracted from the Orphanet database (May 2011).

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 information on rare diseases. 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 medicines agency's internet site (AFSSAPS) publishes 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 SPC and leaflet, updated list of medicinal products available within nominative ATU with specific information if applicable and other general information on hospital preparations.

Since June 2006, the French Health Directorate produces personal health care and information cards in close collaboration with health care professionals and patient organisations, within the scope of the French National Plan for Rare Diseases. These cards are distributed by health care professionals treating the patients concerned, and provide information for health care professionals about the patient and gives brief information on the disease.

In late 2008, the French Minister for Health introduced the outlines of the forthcoming Personal Medical Dossier (DMP). This facultative document, which will concern many rare disease patients (as it is primarily aimed at children, diabetics, those with a chronic illness), should improve the quality of coordination of treatment for both patients and health care professionals, and help information exchange.

In 2010, a new site (droitsdesmalades.fr) designed to inform all of their health care rights, was launched. In addition, the patient organisation Sparadrap¹²⁷ published an informative guide concerning children's rights when they are admitted into health care facilities, including issues such as consent to participate in research and financial aid.

Best practice clinical guidelines

The HAS has produced a number of national diagnosis and best practice guidelines in 2010, including : Immune thrombocytopenic purpura (child and adult), autoimmune hemolytic anaemia, Fabry disease, systemic lupus erythematosus, major adult sickle cell syndromes, major sickle cell syndromes in children, phenylketonuria and toxic epidermal necrolysis (Stevens-Johnson and de Lyell syndromes).

The HAS also published best practice guidelines¹²⁸ for the follow-up of children with deafness under the age of six and their family.

Concerning rare tumors, two national best practice clinical guidelines were published by HAS-INCa, 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, 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 where experts in the field and representatives of rare disease patient organisations are present.

The Paris-based Institute of Myology organised a Summer Programme in 2010: this offers the possibility to train in myology via a condensed 10-day course organised in Paris.

European national conference

On 30 September 2010 the French Alliance Maladies Rares, in collaboration with Eurordis, organised a national conference on rare diseases in the context of the Europlan project. The theme of the conference was "The French plan in the European landscape". The focus of the conference was slightly different than the other Europlan conferences (which aim to reference actions in place already in the field of rare diseases and propose recommendations for a national strategy or plan) as France has already put into action one plan for rare diseases (2004-2008) which was evaluated in 2009. This conference was therefore focused on drawing lessons from the experiences of the first plan for the benefit of other European countries. Amongst the topics of

¹²⁷ <http://www.sparadrap.org/SPARADRAP>

¹²⁸ [http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite de lenfant - 0 a 6 ans - recommandations.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf)

discussion included: ways of measuring the impact of plans (i.e. using databases and registers); the elaboration of the second plan (to be announced before the end of the year); the coding of rare diseases and Orphanet nomenclature; the need for an improvement of training for professionals and information for patients; the need to develop a Foundation for Rare Diseases to advance research in the field; the need to implicate patients in research; ways of improving access to reference and competence centres and orphan drugs. Participants expressed their concern regarding the future of rare diseases in the political agenda, and showed their determination to continue the work underway since the start of the first plan. The final report is now available on line¹²⁹.

National rare disease events 2010

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 towards rare disease research, information services (including the Rare Diseases 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 involving patients and patient organisations. The *Téléthon* and March aim to raise awareness about rare diseases in addition to the Rare Disease Day which is also celebrated.

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.

To mark Rare Disease Day 2010, the French Rare Disease Alliance published a book entitled *Maladies rares, ils témoignent* which compiled statements by rare disease patients on their experience of a particular rare disease. A number of book launches across France took place to mark the event. In addition to this initiative, the members of the French Rare Diseases Platform (*Plateforme Maladies Rares*) – Orphanet, *Alliance Maladies Rares*, *Maladies Rares Info Services*, *Gis-Maladies Rares*, *Association française contre les myopathies* (AFM) and Eurordis, organised a press conference on 18 February 2010 to insist on the importance of a second French National Plan for Rare Diseases with adequate public financing.

On 15 June 2010, *Les Entreprises Françaises du Médicament* – LEEM, organised a conference on the theme ‘Are rare diseases still a priority on France?’¹³⁰. Subject discussed included the progress towards a second French National Plan for Rare, the epidemiology of rare diseases in the development of research and evaluation of needs, as well as the clinical added value of orphan drugs, drug pricing and availability.

On 21 June 2010, Orphanet held its 11th annual forum for patient organisations in collaboration with the French Alliance Maladies Rares at the Groupama Foundation in Paris. This year’s theme was “Communicating with new tools on the internet”: sessions focused on tools for sharing information using the web, tools for communicating with the public, tools proposed by Orphanet for patient organisations, as well as a presentation on registries and the second French National Plan for Rare Diseases. Around 130 participants representing rare disease patient organisations, as well as participants from Orphanet, the Alliance Maladies Rares, Eurordis and Maladies Rares Info Services, attended the event which provided a great opportunity for patient organisations to become acquainted with the improvements in the services provided by Orphanet and tools for communicating using the web.

The new buildings of the French Rare Diseases Platform were officially inaugurated by the French Minister for Health, Roselyne Bachelot, on 21 October 2010. The event was attended by around 140 journalists, scientists in the field of rare diseases, rare disease patient organisation representatives and policy makers, and kicked off with a visit of the new offices, guided by representatives of each of the 6 structures present in the building: Orphanet-INSERM, Maladies Rares Info Services, Alliance Maladies Rares, Eurordis, AFM and Gis-Maladies Rares. The visits gave journalists and stakeholders the chance to see how we work at Orphanet: there were several scientific poster presentations and documentation was on hand for those who wished to learn more about the project. The visit was followed by the official inauguration where the Minister for Health then concluded the speeches by announcing that despite numerous delays the second plan would be unveiled before the end of the year 2010.

The French annual *Téléthon*, organised by the AFM, took place on 3-4 December 2010, raising 90 million Euros, of which a great percentage will be dedicated to research activity in the field of rare diseases. To coincide with this event, the French Rare Disease Alliance organised its annual Rare Disease March on 4

¹²⁹ [http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report_france_europlan.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_france_europlan.pdf)

¹³⁰ <http://www.leem.org/publications/138/les-maladies-rares-sont-elles-encore-une-priorite-en-france-1422.htm>

December 2010 in Paris: around 2000 participants were involved in the event. The year 2010 was, however, a turbulent one for the Téléthon following a number of critics in the national press concerning the management of collected funds and the validity of dedicating a weekend of TV air-time to the event: indeed, the AFM's contract with France Television for the event was not recently renewed (as of the end of 2010).

Other national events included: the Annual Scientific Forum of Stem-Pole (15 November 2010, Evry).

Hosted rare disease events in 2010

Amongst the rare disease related events hosted by France in 2010 and announced in OrphaNews Europe were: Health 2.0 Conference (6-7 April 2010, Paris), EHA-ESH Scientific Workshop: T-cell Acute Lymphoblastic Leukemia Meets Normal T-Cell Development (7-9 May 2010, Mandelieu), 3rd Human Variome Project Meeting: Implementation and Integration (10-14 May 2010, Paris), First International Workshop on Oesophageal Atresia (27-28 May 2010, Lille), International Congress for Tarlov Cysts and Adhesive Arachnoiditis (2-3 July 2010, Chambéry), Future Direction for Orphan Drugs in Europe (3 November 2010, Le Mesnil Amelot), 2nd Health Technology Assessment (HTA) Conference (4 November 2010, Le Mesnil Amelot).

Research activities and E-Rare partnership

Research activities

Public funding is available for rare disease projects from the National Funding Agency for Research (ANR) (basic research) and Health Care Department (PHRC) (clinical research). In addition, some charities and private foundations provide funding for research, such as the AFM's *Téléthon*. 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 *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 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 Funding Agency for Research 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* to facilitate (and fund) access to technology platforms (i.e. genetically modified animal models, high throughput sequencing and 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, the screening and production of stem cells, industrial production of cellular therapies, the creation of laboratories for the production of biomedicines, the running of clinical trials, the 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 Euros to research the field of neuromuscular diseases and rare diseases.

In June 2010, Généthon announced¹³¹ 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).

Other funding opportunities for rare disease research in 2010 included: the 2010 Actelion – SFPC fund for rare disease research; funding from the Line Pomaret Delalande Foundation for doctoral research in the field of rare diseases; the Courtin Foundation's 2010 call for research for chronic inflammatory rheumatism; and a call for projects funded by the French Rett Syndrome Association.

E-Rare

The GIS Maladies Rares is the coordinating partner of the E-Rare ERA-Net for Research Programmes on Rare Diseases, and organised the first joint transnational call in 2007¹³² for research on rare diseases, with the

¹³¹ <http://www.genethon.fr/index.php?id=368>

¹³² http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf

participation of 6 countries and a total of 13 consortia (French teams participated in each of these projects/consortia). France took part in the 2nd E-Rare Joint Transnational Call and France is represented in 11 of the 16 consortia selected for funding in 2009, 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.

Participation in European projects

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). 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, CUREFXS, CLINIGENE, CONTICANET, CONTICABASE, CHEARTED, CRUMBS IN SIGHT, CUREHLH, CRANIRARE, ELAST-AGE, 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, EUORETT, EUROSCA, EURSPA, EUROTRAPS, ENCE-PLAN, EUSTAR, EPOKS, EURO-PADNET, EURIOFNET, FAD, GETHERTHAL, GENESKIN, GENOSTEM, HMA-IRON, HSCR, HAEIII, HUE-MAN, INHERITANCE, IMMUNOPRION, KINDLERNET, LEISHMED, LYMPHANGIOGENOMICS, MANASP, MILD-TB, MITOCIRCLE, MM-TB, MTMPATHIES, MPCM, MITOTARGET, MYASTAID, MYORES, MYELINET, NEUROBID, NEOTIM, NEUPROCF, NMD-CHIP, NOVSEC-TB, NM4TB, NEUROSIS, NEUROPRION, NOVELPID, NEMMYOP, NEUTRONET, NSEuroNet, OSTEOPETR, PODONET, PEMPHIGUS, RATSTREAM, RAPOSDI, RISCA, SKINTHERAPY, STEM-HD, SIOPEN-R-NET, RHORCOD, RDPLATFORM, TB CHINA, THERAPEUSKIN, WHIPPLE'S DISEASE and WHIMPath. France contributes to the following European registries: EUROCARE, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EUROTRAPS, CHS, EUROCARE CF, ECFS, INFEVERS, and TREAT-NMD. France contributes to the EUROPLAN project.

Orphan drugs^{133,134}

Three institutions are involved in the field of orphan drugs on the French market: the French Agency for the Sanitary Security of Health Products (AFSAAPS - *Agence Française de Sécurité Sanitaire des Produits de Santé*), the High Health Authority (HAS – *Haute Autorité de Santé*), 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 mission is research, development, manufacturing and marketing of medicinal products. Rare diseases became priority action in the Leem's strategy in 2002: a rare disease work 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 drugs every year. Since 2001 the LEEM evaluates the advances made in clinical research in France, including clinical research in the field of rare diseases, based on criteria set by the High Health Authority (HAS).

The LEEM published its 2009 social responsibility report¹³⁵ in early 2010 which gave an overview of the state of the art of therapeutic research in the field of rare diseases. Notably, in 2009 ten orphan drugs and/or indications for rare diseases are in the pipeline, a result of an effort since 2002 to include these diseases in the strategies of companies, and of the creation of specialised workgroup at the LEEM on rare diseases which brings together researchers and patient organisation representatives.

Orphan drug committee

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

¹³³ This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

¹³⁴ 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)

¹³⁵ <http://www.leem.org/leem-image/leem/document/1459.pdf>

Orphan drug incentives

Initiatives are in place to stimulate orphan drug development: research support is provided through national funding programmes: *GIS Maladies Rares*, the Hospital Clinical Research Programme (*Programme Hospitalier de Recherche Clinique*); during orphan drug 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 AFSAAPS.

Free scientific advice is available for medicines from the AFSSAPS as well as CT authorisation and compassionate use authorisation (cohort ATU) from AFSSAPS.

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 is one of the initiatives aimed at stimulating research by the pharmaceutical industry into rare diseases in addition to the provisions of the European Orphan Drug Regulation.

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

In October 2010, a proposed law to the finance the French Social Security system included specific provisions for tax exemptions for orphan drugs: the Minister for Health accepted to raise the threshold for tax exonerations to orphan drugs, which was initially foreseen to be fixed at €20 million. This threshold will now be raised to orphan drugs 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 drugs from certain regulations, and that for orphan drugs 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.

Orphan drug availability

According to the registry of the French Agency for the Sanitary Security of Health Products (AFSSAPS) website, the availability of orphan drugs in France can be represented as follows:

- Orphan drugs with valid market authorisation and with mention of commercialisation: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Onsenal, Orfadin, Pedeia, Photobarr, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tassigna, Thalidomide Celgene, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Vpriv, Wilzin, Xagrid, Yondelis, Zavesca.
- Orphan drugs with valid market authorization without mention of commercialisation: Ceplene, Mepact, Siklos, Tepadina.

Orphan drug reimbursement policy

The *KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* highlights that "*Treatment and reimbursement is decided upon by decree of the Ministers of Health and Social Security and following advice of the National Union of the Sickness Funds. The specialities, products or services being the subject of the decree can be dealt with only if their use is essential to the improvement of the health of the patient or to avoid worsening of the condition. They must also be registered explicitly in the treatment protocol.*"¹³⁶

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*¹³⁷, "*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 Social Security made it obligatory for the first prescription

¹³⁶ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p47)

¹³⁷ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p14)

for an orphan drug to be validated by a 'centre de référence' designated for the patient's rare disease when available, or by the 'centre de compétence' directly linked to the 'centre de référence'.

In 2005, and in March 2008 two decrees came into action concerning the exceptional coverage of off label use by the national insurance of certain pharmaceutical products or services intended in particular for rare diseases. These decrees allow for the coverage of these drugs or services, for a respective 4-year or 3 year renewable period in case of acceptable situations.

Other initiatives to improve access to orphan drugs

The *KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* highlights that "off-label use of an orphan or non-orphan drug is possible for a rare disease (as defined by the European Regulation 141/20005) if the medicinal product is listed in an advice or recommendation relating to a category of sick persons of the HAS (Article L162-17-2-1 of the Social Security Legal Code)."¹³⁸

Compassionate use for individual patients takes the form of either cohort use or named patient supply prior authorisations (nominative ATU) 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 orphan 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) will be 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 an overview in its 2009 activity report¹³⁹, published in 2010, of the « Autorisations Temporaires d'Utilisation » (ATU) (Temporary Use Authorisations) discerned and the « Plans d'Investigations Pédiatriques » (PIP) (Paediatric Investigation Plans): these two areas concern the field of rare diseases and orphan drugs. In 2009, for the 9 orphan drugs with a new European marketing authorisation, 6 were already available within the ATU system. The AFSSAPS also established a national public register of clinical trials on medicines conducted in France in September 2009, which is regulatory updated.

Orphan drug pricing policy

The accelerated process for pricing has been reduced to 15 days.

Orphan devices

No specific information reported.

Specialised social services

Respite care services are available for patients whose care is demanding on their relatives: this is only partially reimbursed for certain rare diseases (through the "ticket modérateur"). 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 certain services provided by patient organisations all aim to assist the integration of rare diseases patients 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.

¹³⁸ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p47)

¹³⁹ http://www.google.fr/url?sa=t&source=web&cd=1&ved=OCBsQFjAA&url=http%3A%2F%2Fwww.afssaps.fr%2Fcontent%2Fdownload%2F27233%2F361595%2Fversion%2F1%2Ffile%2FAfssapsRA09.pdf&rct=j&q=AFSAPPS%202009%20RAPPORT&ei=VBJUTaizlsuq8QQunbDwBw&usg=AFQjCNGGuawHRIFU6hBt48vanDu3lz7H_Q&sig2=8G4CILXOx_sG425WAES7gA&cad=rja

1.10. GERMANY

Definition of a rare disease

Stakeholders in Germany accept the European Orphan Drug Regulation 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 of high quality and the access to medical doctors and specialists is (independent of the disease's incidence) good. 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: a study entitled 'Strategies for improving the health care situation of patients with rare disease in Germany' has been commissioned by the Federal Ministry of Health. Its goal is to focus on existing measures and to refine them by involving all key bodies and organisations of the German health care system.

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

The Federal Ministry of Health in Germany initiated a national action league for people with rare diseases - *Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen* (NAMSE)¹⁴⁰ – 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.

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.

¹⁴⁰ <http://namse.de/>

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'.

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.

Legislation provides the basis for the contracting of *Hochspezialisierte 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. 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.

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 currently built up [funded by the Federal Ministry of Education and Research (BMBF)] will attempt to register 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, 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 by stipulating that laboratories be accredited.

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 1387 genes and an estimated 1406 diseases in the Orphanet database¹⁴¹.

National alliances of patient organisations and patient representation

In Germany, the German National Alliance for Chronic Rare Diseases (ACHSE) regroups more than 70 patient organisations. Through ACHSE, rare disease patient organisations support each other, exchanging know-how so as to strengthen their influence in the political arena. ACHSE organised a range of events for Rare Disease Day 2010 (see section “National rare disease events”). The alliance also produced a new information brochure in 2010 which included information on using Orphanet.

In Germany, health-related self-help is eligible for financial support from the statutory health insurance funds since 2000. 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.

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.

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 German¹⁴² 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 country site was launched¹⁴³. 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.

Other sources of information on rare diseases

All medicinal products, including orphan drugs, are included in a database called AMIS, run by the German Institute of Medical Documentation and Information (DIMDI)¹⁴⁴ ensuring public information in the field.

The ACHSE website¹⁴⁵ 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

¹⁴¹ Information extracted from the Orphanet database (May 2011).

¹⁴² www.orphanet.de

¹⁴³ <http://www.orpha.net/national/DE-DE/index/startseite/>

¹⁴⁴ www.dimdi.de/static/de/amg/amis/index.htm

¹⁴⁵ www.achse.info

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 KINDERNETZWERK¹⁴⁶ 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 website¹⁴⁷ (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 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: Roche Lexicon (www.tk.de/rochelexikon) private company, 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 Schering AG), ONKODIN (www.onkodin.de) with focus on hematological diseases, public funding, www.patienten-information.de (www.patienten-informationen.de) of the ÄZQ (Medical Centre for Quality) – an initiative of the Bundesärztekammer (Federal Society of Physicians) 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 neurogenerative diseases and the laboratories that are apparently qualified for diagnosis (Funding is unclear.). About 100 rare diseases are described within this database from a private company (goFeminin.de GmbH) in the Onmeda database (www.onmeda.de). 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.

Best practice clinical 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*).

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

Europlan national conference

On 13 & 14 October 2010 in Berlin the German National Conference on Rare Diseases¹⁴⁸ was organised by ACHSE in collaboration with Eurordis within the scope of the Europlan project. More than 180 representatives of patient organisations, researchers, funding agencies, health policy makers and rare disease clinicians gathered to discuss on the transposition of the European policy framework and recommendations into a national strategy for Germany. All stakeholders showed great interest in the sessions that covered a broad field of themes reflecting the current national situation for patients with rare diseases in Germany. Specific measures were proposed during 4 parallel workshops entitled “Health Care”, “Information”, “Research” and “Monitoring of a National Plan of Rare Diseases”. The final report is available online for public consultation¹⁴⁹.

National rare disease events in 2010

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Paediatric

¹⁴⁶ www.Kindernetzwerk.de

¹⁴⁷ www.nakos.de

¹⁴⁸ <http://www.achse->

online.de/cms/was_tut_achse/interessen_vertreten/nationale_konferenz_okt_2010.php&rurl=translate.google.fr&twu=1&usg=ALkjrhhTBGjv2I5J9sR5VFOi6sVxlc3iiQ (accessed 28/01/11)

¹⁴⁹ http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_german_europlan.pdf

endocrinology and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2010 events were organised in Berlin, Bielefeld, Dresden, Essen, Hamburg, Hannover, Cologne, Magdeburg, Stuttgart and Würzburg by different patient organisations. These events were aimed at raising awareness and informing the public about the problems and needs of people living with rare diseases. The Eva Luise and Horst Köhler Foundation for People with Rare Diseases in cooperation with ACHSE awarded the Eva-Luise-Köhler-Forschungspreis for a research project.

A Rare Disease Day Symposium was organised by Orphanet Germany at Hannover Medical School (MHH) on 26 February 2010. This event was well attended and about 30 different support groups took part in the symposium either by giving talks and/or presenting information stands. The scientific community was also represented by professionals from the MHH, giving information about their experience and daily work on rare diseases. Altogether 21 interesting talks covering different topics in the field of rare diseases were presented by the representatives of associations, clinicians and researchers. The topics included: the latest scientific developments in gene therapy, the problems of fund raising. About 200 people visited this event and the press also attended the meeting: the local print media published a report concerning the events of the day and there was also television coverage of the event.

On 2-4 March 2010 a three day Conference of the German Society of Human Genetics (GfH) was held in Hamburg. Between 800-900 people attended this annual event representing a wide range of human genetic professional disciplines. Invited experts from basic science, clinical and social care give presentations within educational sessions, symposia and workshops.

Hosted rare disease events in 2010

Amongst the rare diseases events hosted by Germany and announced in OrphaNews Europe were: the Second Congress of the European Society for Paediatric Anaesthesiology (2-4 September 2010, Berlin) where a whole session was dedicated to rare diseases, the 2nd Pan-European Conference on Haemoglobinopathies (13-14 March 2010, Berlin), the TREAT-NMD Clinical Trials in Neuromuscular Disorders and Other Rare Diseases Workshop (24-26 June 2010, Freiburg), the Tuebingen Outer Retina Conference (29-31 August 2010, Tuebingen, Germany), the Syringomyelia 2010: International Symposium (9-11 December 2010, Berlin, Germany).

Research activities and E-Rare partnership

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.

Additional funding of rare disease research is ongoing in other funding initiatives of the BMBF such as the National Genome Research Network (NGFN), the Competence Networks for Medicine, Innovative Therapies, Clinical Trials and others with about €20 million in 2010. 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 Seltene Erkrankungen*, a foundation of the First Lady and the 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.

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 first E-Rare joint transnational call in 2007 and funds the participating German research groups of 10 transnational research projects with a total €3.3 million funding. Germany also participated in the second transnational call in 2009 for which PT-DLR managed the joint call secretariat. The BMBF is funding the participating German research groups of 14 transnational research projects with €3.2 million. Germany is currently participating in the 3rd Joint Transnational Call.

Participation in European projects

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). 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, EMVDA, ENRAH, ENCE-PLAN, EURADRENAL, EUCILIA, EUNEFRON, EURIPFNET, EUROBONET, EUROBFNS, EUROSD, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROSCA, EUROTRAPS, EURORETT, EUROSPA, ERMION, EuPAPNet, EUBNFS, EURO-CGD, ELA2-CN, EMINA, EPINOSTICS, EUREGENE, EUROPEAN LEUKEMIA NET, EMSA-SG, ESDN, FASTEST-TB, GETHERTHAL, HMA-IRON, HAE III, HDLOMICS, HUE-MAN, HMANASP, INTHER, KINDLERNET, LEISHDRUG, MANASP, MITOTARGET, MYORES, MIMOVAX, MOLDIAG-PACA, NEUROSIS, NSEuroNet, NEUTRONET, NEMMYOP, NEWTBDRUGS, PULMOTENSION, OVCAD, OSTEOPETR, PODONET, PEMPHIGUS, RD PLATFORM, RevertantEB, RHORCOD, RATSTREAM, RISCA, WHIPPLE'S DISEASE and TB-VIR. German teams contribute to the following European registries: EUROCAT, TREAT-NMD, EBAR, EHDN, EurIPFnet, EURIPEDES, European Alport registry, EUROSCA-R, EUTOS and RegiSCAR. Germany contributes to the EUROPLAN project.

Orphan drugs**Orphan drug committee**

No specific information reported.

Orphan drug incentives

No specific activity reported.

Orphan drug availability

No specific information on the orphan drugs marketed in Germany has been reported.

Orphan drug reimbursement policy

Once authorised at European level, all orphan drugs are fully reimbursed by the statutory health insurance (*GKV*). Due to the specific characteristics of several drugs the German Joint Federal Committee decided in October 2008 to implement additional requirements for the prescription procedure concerning the qualification of the physicians and the documentation of the therapy. Up to now, these requirements apply to one rare disease (pulmonary arterial hypertension).

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 therapeutical 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 drugs authorized 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 drugs

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 effects.

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. Once authorized, all orphan drugs are fully reimbursed by public health insurance.

Orphan drug pricing policy

All orphan drugs are reimbursed directly after market authorisation. As the German maximum reimbursement prices scheme (Festbeträge) normally does not cover orphan drugs, they were excluded from any on reimbursed prices. Only generic products and those considered to belong to the same pharmacological or therapeutic group can be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, for every new drug with patented or non-generic substances a binding ex-factory price based on the value of the drug have to be negotiated on Federal Level. This is carried out by the Federal Association of Sickness Funds and the manufacturer. If no agreement can be achieved, the price is set by arbitrage committee, in which both contract parties are represented. For the first 12 months following marketing authorisation each new drug is still reimbursed at the full price set by the manufacturer. Mandatory Price Negotiations have been introduced by the Act for the New Order for the Drug Market in Social Health Insurance (AMNOG). According to this law, previous to price negotiations the value of the drug is evaluated. The manufacturer issues a Dossier when they enter the market. It is assessed by the German Institute for Quality and Efficiency in Health Care (IQWiG). The Federal Joint Committee (G-BA) appraises and decides on the added value of the drug compared to standard therapy. For Orphan drugs authorized by EMA under EU-regulation 141/2000 with an annual turnover below 50 million are manufacturers are freed from the obligation to proof an added value, because the additional benefit is taken as granted. Still, price negotiations are mandatory also for these drugs.

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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals; however no official definition has been proposed or accepted.

National plan/strategy for rare diseases and related actions

The national objectives for the care of rare diseases have been incorporated into the existing structure of the national health system. A commission composed of government officials, health professionals and patient representatives was formed in 2007 following requests buy 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 Disorders (to run over the period 2008-2012¹⁵⁰) 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),

¹⁵⁰ http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf

- 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.

Although an initial estimate for the budget required was made, no funding has been officially allocated to the National Plan of Action for Rare Disorders, and none of the eight strategic priority actions have yet started. As of yet, there is no legal framework for the Plan.

The provisions of the Greek National Plan for Rare Diseases (2008-2012) were discussed in detail during the Greek National Conference on Rare Diseases 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 (see section "Europlan national conference").

Health services already provided by Greek National Health Service 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 paediatricians 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 in 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 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 of 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, sickle cell anaemia, etc.) 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) has started to collect data on the nature and activities of these units and aims to complete collection of this data in 2011. Greece is working to provide better access to treatment for rare disorders, including the accreditation and creation of centres of expertise for rare disorders: an action in this direction was notably recommended at the Greek National Europlan Conference by stakeholders.

Registries

There is currently no national registry for rare diseases in Greece. A new Scientific Committee mainly consisting of clinicians caring for patients with rare diseases was appointed in December 2010 by the Hellenic Centre for Disease Control and Prevention (KEELPNO) and one of its main tasks is to set up a national registry, according to the international standards.

Greek teams contribute to the European registries EUROCARE CF and EUROWILSON.

Neonatal screening policy

Neonatal screening is provided by the Institute of Child Health, Athens, for congenital hypothyroidism, phenylketonuria, G6PD deficiency and galactosaemia. In Greece, the neonatal screening offer 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.

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.

Diagnostic tests are registered as available in Greece for 104 genes and an estimated 160 diseases in the Orphanet database¹⁵¹.

National alliances of patient organisations and patient representation

In Greece, PESPA (the Greek Alliance for Rare Diseases) is an umbrella non-profit organisation established in 2003, established by health professionals and presidents of rare disease patient associations with the help of Eurordis. There are currently no public funding schemes to support patient organisation 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. The translation of the Orphanet website and encyclopedia of diseases in Greek has been allocated 10 000€ by the Hellenic Centre for Disease Control and Prevention following a request made in 2010 by the Greek Ministry of Health and Social Solidarity.

Official information centre for rare diseases

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

Help line

There is currently no official help line for rare disease information in Greece, but some services are provided by members of PESPA and other patient organisations (mainly volunteers), which provide psychological support and general information to callers.

Other sources of information

The PESPA website offers information on rare diseases and a list of some rare diseases in Greek. Every "special" unit produces information leaflets for the disease(s) of its expertise.

Best practice clinical guidelines

Some scientific societies have published 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.

Europlan national conference

On 26-27 November 2010, the Greek National Conference on Rare Diseases, organised by PESPA and Eurordis was held in Athens in the framework of the Europlan project. The conference was held at the Eugenides Foundation, Athens, under the patronage of Chairman of Greek Democracy Karolos Papoulias and was attended by over 350 people, from all the main stakeholders in Greece, such as representatives of the Ministry of Health and Social Solidarity, Ministry of Labour and Social Security, Health Insurance Departments, the Hellenic Centre of Infectious Disease Control and Prevention, the General Secretariat for Research and

¹⁵¹ Information extracted from the Orphanet database (May 2011).

Technology of the Ministry of Education and Life Long Learning, Secretary General of the Greek Association of Pharmaceutical Companies, Vice-President of the Greek Association of Biotechnology, the National Organisation of Pharmaceuticals, academic professors, healthcare professionals (doctors, nurses, psychologists etc), the representatives of Orphanet in Greece, researchers in the field of RD, students, representatives of patient associations, patients and their families and the general public. Most of the members of the public who participated were interested in finding a solution to their family members' health issues. The National Plan for Rare Diseases (2008-2012) was discussed in detail during the workshops and it was highlighted by the participants that: there is a lack of committee or coordinating body to monitor/evaluate the National Plan; the Plan also has no legal framework; there is a lack of public awareness of the Plan; and there is no budget or no allocated source of funding for the Plan. 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 drugs, 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 drugs 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. The final report is now publically available online¹⁵².

National rare disease events in 2010

In 2010 the Greek Alliance PESPA (as every year since its establishment in 2003) organised a number of events in Greece for Rare Disease Day: firstly a public visit of the two biggest pediatric hospitals in Athens, the Aghia Sophia Children's Hospital and the Aglaia Kyriacou Children's Hospital on 26 February 2010, followed on 27 February 2010 by an all-day "happening", including the distribution of information material on Rare Diseases in the Shopping and Commercial Centre "The Mall" in Athens. There were events and scientific presentations dedicated to Rare Disease Day at the Eugenides Foundation 28 February 2010 and in addition there were TV and radio spots on National TV channels and radio stations. Announcements prior to the Rare Disease Day were directed toward the scientific and medical community at National Research Centers, University Departments and Hospitals with the slogan "Bridging Patients and Researchers".

Hosted rare disease events in 2010

There were no rare disease events hosted in Greece in 2010.

Research activities and E-Rare partnership

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.

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 it is ongoing. Greece currently participates in E-Rare-2, and is represented by two institutions: GSRT and the Hellenic Center for Disease Control and Prevention (HDCCP). GSRT has participated in the 3rd Joint Transnational Call in the context of E-Rare 2 launched in autumn 2010.

Participation in European projects

Greece participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, EUROHISTIONET, EN-RBD and TAG. Greece participates, or has participated, in European rare disease research projects including: BIOMALPAR, BNE, EPINOSTICS, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EVI-GENORET, GEN2PHEN, GETHERTHAL, HDLomics, ITHANET, MYASTAID and NEUROPRION. Greece contributes to the following European registries: EUROCARE CF registry. Greece contributes to the EUROPLAN project.

¹⁵² http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report%20Greece%20EUROPLAN%202010.pdf (accessed 28/01/2011)

Orphan drugs

The Greek National Organisation for Medicines (EOF¹⁵³) ensures the public health and safety of all medicinal products, including Orphan Drugs. Orphan drugs 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 drug committee

No specific information reported.

Orphan drug incentives

No specific information reported.

Orphan drug availability

Of the orphan drugs authorised by the EMA, 41 are readily available on the Greek market, whereas 11 more are imported by the Greek Institute of Pharmaceutical Research and Technology. The remaining drugs have never yet been requested by Greek patients, but if they were requested, they would be imported by the Greek Institute of Pharmaceutical Research and Technology.

The following orphan drugs are readily available on the Greek market: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Cayston, Evoltra, Exjade, Fabrazyme, Firazyne, Flioland, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Nexavar, Nplate, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Siklos, Somavert, Sprycel, Tassigna, Thalidomide Celgene, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Xagrid, Yondelis, Zavesca.

Orphan drug 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*¹⁵⁴), 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 drugs

There are currently no programmes to facilitate access to Orphan drugs. The Greek Alliance PESPA has put in place some awareness raising campaigns concerning orphan drugs.

Orphan drug pricing policy

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Patients have limited access to respite care services, but these are not specifically for rare disease patients. The patients sometimes have to financially contribute to these services which are run by national institutions, patient associations and non-governmental organisations. A few therapeutic recreational programmes are available, organised by the same types of organisations, and the patient must also financially contribute to this. Limited help with household chores, psychological support, help with shopping and mobility assistance can be sought by patients with special needs (suffering from rare diseases or not) and are provided by local authorities or NGOs. PESPA provides some psychological support (with the help of professionals who are voluntary) to patients with rare diseases and their families.

¹⁵³ <http://www.eof.gr>

¹⁵⁴ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

1.12. HUNGARY

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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 is a part of the National Public Health Institute, and is empowered to investigate quality related issues in health care, public health consequences of health care operation, and to initiate interventions if needed. The NRDC network participates in preparation of recommendations for Governmental health authorities in the fields of:

- 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 drug 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, 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 NRDC makes use of the National Centre for Healthcare Audit and Inspections' IT centre facilities 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 National Institute of Pharmacy. 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).

Despite this initiative, there is currently no plan for rare diseases in Hungary, and no Committee in place to elaborate and implement such a plan. The NRDC does not have the authority to develop a national plan. At the Europlan national conference on rare diseases, 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.

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.

OSZMK is initiating 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 National Centre for Healthcare Audit and Inspection has also initiated an open registry concerning the activities of centres of care and expertise, including the activities of consultants and laboratories requiring accreditation.

A HURO-euro programme plan is in process for a number of Hungarian centres in which the Universities of Szeged and Debrecen have jointly submitted a tender with Romanian establishments to work on the establishment of centres of expertise.

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 and EURO CARE CF.

Neonatal screening policy

A compulsory, government-financed newborn screening program covering the whole country has been running since 1975, and after introduction of tandem mass spectrometry screening in 2007, now includes 26 diseases, amongst which phenylketonuria, hypothyroidism, galactosaemia and biotinidase deficiency which belong to the classic core. Two centres are responsible for the operation of this nationwide network.

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 database¹⁵⁵.

National alliances of patient organisations and patient representation

The Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS) is the national alliance of rare disease patient organisations in Hungary, affiliated with Eurordis. HUFERDIS is currently encouraging the

¹⁵⁵ Information extracted from the Orphanet database (May 2011).

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 participates in the development of National Plan, 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.

Following a collaboration established between HUFERDIS, NRDC and the Hungarian Orphanet team, the EurordisCare 2 and 3 surveys were carried out implemented in Hungary. HUFERDIS takes part in the several international projects including Europlan, POLKA, BURQOL-RD, Rare Disease Days, etc.

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 Pecs. This team 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 (www.orpha.net) 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

A website is maintained by the government (www.oszmk.hu) which has a limited amount of information concerning rare diseases. Scientific societies (www.humangenetika.hu), HUFERDIS (www.rirosz.hu), non-governmental expert groups (www.betegmagzat.hu) and market-based organisations (www.webdoki.hu) have web based services for patients.

Best practice clinical 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 (e.g. Williams syndrome).

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 has been organising 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.

Europian national conference

HUFERDIS organised with Eurordis a National Conference on Rare Diseases (18-19 October) in Budapest in the scope of the Europlan project. All stakeholders were present during the two day conference aimed at defining concrete steps to develop a national action plan for rare diseases. 148 participants took part in the two day event including experts, patients and representatives of government and the Industry. The final report is available online¹⁵⁶.

Participants at the conference determined 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 via the OSZMK webpage, 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.

National rare disease events in 2010

The Orphanet Team and the NRDC are involved in Rare Disease Day events, which are organised by HUFERDIS. HUFERDIS, the Hungarian rare disease alliance, organised a public event on 28 February 2010 in Budapest at Heroes' Square which included entertainment and information on rare diseases.

The Conference of the Hungarian Society of Human Genetics (Debrecen, September 2010) was another major event in the field of rare diseases.

Hosted rare disease events in 2010

No specific activities reported.

Research activities and E-Rare partnership

Research activities

Research funds for rare diseases are available from the Hungarian Scientific Research Fund for Rare Disease Research.

In Hungary, 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. Where previously rare diseases were not one of the priority areas, but many rare diseases related grants were financed (e.g. governmental supported the project on the periconceptional folate status and on attitude towards different supplement programs), rare diseases are now a priority for research. 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 program¹⁵⁷. 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. 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 are expected 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

¹⁵⁶ [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)

¹⁵⁷ <http://www.molneur.eoldal.hu/cikke/englis>

the Orphanet data collection standards. The system has been launched and the primary database will be used to contribute to the Orphanet database.

E-Rare

Hungary is full partner of E-Rare-2 via the National Rare Disease Research Coordinating Centre at University of Pécs.

Participation in European projects

Hungary participates, or has participated, in the following European Reference Networks for rare diseases: EPNET/EPI and Care-NMD. Hungary participates, or has participated, in European rare disease research projects including: BNE, EUROBONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROSICA, EUROWILSON, GENESKIN, NMD-CHIP, TREAT-NMD, SCRIN-SILICO, BBMRI and SIOPEN-R-NET. Hungary contributes to the following European registries: EUROCARE CF, EUROCAT and TREAT-NMD. Hungary contributes to the EUROPLAN project.

Orphan drugs¹⁵⁸

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 drug committee

There is no committee for orphan drugs in Hungary

Orphan drug incentives

No specific activity reported.

Orphan drug availability

70% of orphan drugs with an EU market authorisation are on the market in Hungary. The orphan drugs on the market in Hungary are: Afinitor, Aldruazyme, Arzerra, Atriance, Ciclosporin, Cystadane, Diamcomit, Dudopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Onsenal, Orfadin, Pedeia, Photobarr, Prialt, Replagal, Revatio, Revlimid, Revolade, Somavert, Sprycel, Tasigna, Thelin, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votrient, Wilzin, Yondelis, Zavesca. Availability of orphan drugs varies from region to region. In the case of rare cancers, orphan drugs are available via assigned oncological centres.

Orphan drug reimbursement policy

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal product¹⁵⁹*, "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"¹⁶⁰. 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 drugs are 100% reimbursed in Hungary.

¹⁵⁸ 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)*

¹⁵⁹ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)*

¹⁶⁰ *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)*

Other initiatives to improve access to orphan drugs

Off-label use is possible, provided that the benefits of the drugs for a certain disease are certified, but the process is highly bureaucratic.

Orphan drug pricing policy

The OEP does not have a direct impact on pricing.

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, these programmes do not, however, cover the whole country. The national strategy "Our common treasure, the child" gives overall concepts of principals of integrating and developing children living with disabilities, but no action programme is linked to this. 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. 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.

1.13. IRELAND

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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 Planning 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 national plan, starting with a mapping exercise and focusing on the structure, governance and monitoring of a national strategy. The Group held their first meeting in April 2011.

On 20 January 2011 the Genetic and Rare Disorders Organisation in collaboration with Eurordis organised a National Conference on Rare Diseases in the scope of the Europlan project (see section "National rare disease events").

The Irish Council for Bioethics ceased to operate on 1 December 2010, as a result of a Government decision to discontinue funding the operation of the Council. However, the Council's three professional staff were seconded into the Department of Health and Children (DOHC) to work specifically on bioethics-related topics. Furthermore, the DOHC is currently formulating proposals with regard to establishing a national bioethics advisory body for Ireland, which would operate under the auspices of the DOHC and would be tasked with considering bioethical issues pertaining to the healthcare area.

Centres of expertise

Currently, the Irish Department of Health and Children has no specific list of national centres of expertise, nor does it set standards for specific units to be considered "national". However, the department does recognise that particular centres have particular expertise, and would give specific funds to support those specialist services. The Health Service Executive 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 comprehensive 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.

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) has created a Steering Group 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 is 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. This research will also shed some light on the existence and quality of rare disease patient registries in the country. A Health Information Bill is expected to be published in 2011 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.

Neonatal screening policy

Neonatal screening is in place for galactosaemia, hypothyroidism, phenylketonuria, homocystinuria and maple syrup urine disease. The current Director of the National Newborn Screening Programme is working with the Department of Health and Children to expand the newborn screening programme. Neonatal screening for cystic fibrosis is scheduled to commence during summer 2011.

Genetic testing

Genetic testing in the Republic of Ireland is available through the National Centre for Medical Genetics (NCMG)¹⁶¹, Our Lady's Hospital, Crumlin, which processes approximately 13,000 cytogenetic and molecular genetic tests annually. The cytogenetic and molecular genetics laboratories are externally accredited by CPA (UK). The National Centre for Medical Genetics is publicly funded via the Irish Health Service Executive. 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 19 diseases in the Orphanet database¹⁶².

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. The organisation is 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.

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.

Official information centre for rare diseases

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

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.

¹⁶¹ <http://www.genetics.ie/>

¹⁶² Information extracted from the Orphanet database (May 2011).

Other information on rare diseases

Public information about rare diseases is also provided by patient organisations and the GRDO. The MRCG supports smaller patient groups 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 Group¹⁶³. 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 Family¹⁶⁴.

Best practice clinical guidelines

Clinical guidelines exist for certain diseases.

Training and education initiatives

No specific information reported.

Europlan national conference

On 20 January 2011 a National Conference on Rare Diseases¹⁶⁵ was held in Dublin in the scope of the Europlan project. Organised by the, the Genetic Rare Disorders Organisation (GRDO), the Medical Research Charities Group (MRCG) and the Irish Platform for Patients' Organisations Science & Industry (IPPOSI), the conference featured presentations and speeches by rare disease patients, scientific and medical experts, patient organisations, , the Orphanet UK and Ireland team and health officials. Four working sessions were organised around the themes of centres of expertise, orphan drugs and access to treatments, research and patient empowerment and support. 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, according to Dr John Devlin, Deputy Chief Medical Officer at the Department of Health. Speaking at the event, Dr Devlin said the groundwork had been laid for discussion of all the main issues surrounding rare diseases. These include: developing centres of expertise, development of research on rare diseases; access to therapies and treatments and patient empowerment. The final report is now available online¹⁶⁶.

National rare disease events in 2010

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 drugs. IPPOSI, the Genetic and Rare Disorders Organisation (GRDO) and the Medical Research Charities Group (MRCG) held a meeting on 25 February 2010 to mark Rare Diseases Day. The meeting entitled *"Patients and Researchers: Partners for Life"* brought together speakers from all sectors in Ireland and Europe to look at diagnosis, treatment and access to medicines for people with a rare diseases. This event aimed to bring all relevant and interested stakeholders together to begin to address this deficit in the area of Irish rare disease policy and to move this process forward. An executive summary report¹⁶⁷ of the conclusions of the day was released on the 24 November 2010 which included the recommendations of the group of the next steps to take in the development of a national plan for rare diseases in Ireland.

¹⁶³ <http://www.rehab.ie/index.aspx>

¹⁶⁴ <http://www.cafamily.org.uk/index.php?section=861>

¹⁶⁵ <http://www.europlan.ie/>

¹⁶⁶ http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_ireland.pdf

¹⁶⁷ http://www.ipposi.ie/index.php/component/docman/doc_download/56-final-rare-disease-report-2010 (accessed 29/01/2011)

Hosted rare disease events in 2010

Amongst the events hosted by Ireland in the field of rare diseases and announced by OrphaNews Europe where: the Scientific Meeting of the International Network of Paediatric Surveillance (7 October 2010).

Research activities and E-Rare partnership

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"¹⁶⁸.

E-Rare

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

Participation in European projects

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. 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. Ireland contributes to the following European registries: EUROCAT and EURO CARE CF. Ireland contributes to the EUROPLAN project.

Orphan drugs

Orphan drug committee

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

Orphan drug incentives

This will be covered in the National Rare Disease Plan.

Orphan drug availability

This will be covered in the National Rare Disease Plan.

Orphan drug reimbursement policy

This will be covered in the National Rare Disease Plan.

Other initiatives to improve access to orphan drugs

This will be covered in the National Rare Disease Plan.

Orphan drug pricing policy

This will be covered in the National Rare Disease Plan.

Orphan devices

This will be covered in the National Rare Disease Plan.

¹⁶⁸IPPOSI Information Document on Rare Diseases – 19 February 2009
<http://www.ipposi.ie/index.php/information-centre/rare-diseases>

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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10,000 individuals.

National plan/strategy for rare diseases and related actions

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 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. Decree 279/2001 provides for a regular update of such list, even if to date no update has been carried out. In four Italian Regions, legislative acts extend the number of rare diseases in this list. The implementation of the regional actions on rare diseases receives funding from the Ministry of Health. Provision of services for rare diseases and orphan drugs follows the distribution of responsibilities described above. A Committee ensures the interregional coordination for rare diseases between the Ministry of Health, the *Istituto Superiore di Sanità* (National Institute for Health, ISS), and all Italian Regions. This Committee has several aims, which include harmonisation of the regional 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 projects aimed at strengthening the regional 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 drugs, aimed at the prevention, treatment and surveillance of these diseases. This Centre took over the activities carried out for many years by a specific unit within the ISS to tackle rare diseases (www.iss.it/cnrmr).

On the occasion of the "*Conferenza Stato-Regioni*" on 26 February 2009, the State Secretary for Health (and now Minister of Health) Professor Ferruccio Fazio communicated that €8 million would be allocated to Rare Diseases: €5 million from Ministry of Welfare and €3 million from AIFA (the Italian Drug Agency).

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 n. 279/2001, all LEA services are totally free for citizens affected by a rare disease included 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 to the others. The LEAs, first defined in 2001, have been updated recently by the Ministry of Health, allowing progress in quality, appropriateness and efficiency and including not only a new list of a further 109 diseases, but also a list of procedures (for example, laboratory assays for the diagnosis of metabolic diseases). At present, this act has not yet come into force because the Ministry of Finance is assessing its feasibility.

An agreement has been signed between the Government, the Regions and the special statute Provinces of Trento and Bolzano 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 diseases in Florence in the context of the EUROPLAN project (see section "National rare disease events").

On 21 April 2010 senator Laura Bianconi presented a new draft of laws n° 52, 7, 146, 727, 728, 743, focusing on the incentives for research and access to therapies for rare diseases and the production of orphan drugs. This act has to be discussed by the Parliament and its approval lies outside the direct domain of the Ministry of Health.

Centres of expertise

In 2001 the Ministerial Decree 279/2001 foresaw the setting up 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, over 250 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.

In each Region a Regional and Interregional Coordination Centre has been (or should be) created, in order to manage the activities of referral centres, to exchange information between them, and to provide expertise and data to the regional rare diseases registries. If a patient is suspect to have a rare disease, the patient is addressed to designated hospitals where a free of charge diagnosis can be achieved and, if the disease is confirmed, free treatment is offered by any hospital or outpatient facility within the NHS (Ministry Decree n. 279/2001).

Registries

The National Registry of Rare Diseases (NRRD) was established at ISS in 2001 in accordance with article 3 of Ministerial Decree 279/2001. This registry collects clinical, biochemical, demographic, risk factors, lifestyle and other data relevant for scientific purposes and research. The Registry aims at obtaining epidemiologic information (in the first place, the number of cases of a specific RD and the related distribution on National territory), and other useful information to evaluate problems in the field of rare diseases; it is also a tool for the monitoring of the delays in diagnosis and patient migration (from one Region to another and from Italy to other countries and vice versa), to support clinical research and to promote discussion amongst health professionals regarding the definition of diagnostic criteria.

Some Regions have developed independent registries; other Regions have adopted informatics tools developed out by the NCRD. In particular, in 2007 this Centre put into action a new method of data collection: new software which can run either in separate medical centres qualified to diagnose and treat rare diseases patients, or in those in charge of coordinating regional activities and providing the liaison with the NCRD.

Independent registries have been developed by the Veneto (see below), Tuscany, Piedmont, and Lombardy Regions.

The model established by the Veneto Region has been also implemented by Friuli-Venezia Giulia, Trentino-Alto Adige, Emilia Romagna, and Liguria. Veneto's model is based on an informatics infrastructure acting as a network connecting different Centres involved in the management of patients with rare diseases. All the steps concerning diagnosis, clinical follow-up and treatment are linked by a unique information system shared by all those involved in patients' management.

All regional Registries collect epidemiological information and every 6 months send the agreed common data set to the NRRDs at ISS.

Until 31 March 2010, a total of 94.185 cases and 485 different rare disease had been recorded in the Italian NRRDs. Registered disorders include nervous system diseases 21.05%; blood and blood-forming organs diseases 20.6%; endocrine, nutritional and metabolic diseases 18.95%; congenital malformations 15.04%.

The National registry is linked to other interregional, regional and international registries.

Italy also participates in European registries such as EUROCAT, 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.

Some 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.

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 Genetics Institutes. 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 Institutes. Data collection takes into account the typology of the Institutes, personal details, 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.

ISS is in charge of carrying out External Quality Control (CEQ) for genetic tests. CEQ activity includes molecular and cytogenetic tests and has been addressed to public laboratories which use genetic tests. The CEQ 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.

In 2010, in collaboration with SIGU, a group of experts determined that changes were needed to improve the organisation of genetic services¹⁶⁹. 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 691 genes and an estimated 788 diseases in the Orphanet database¹⁷⁰.

Within the national framework there are consolidated procedures to send biological and genetic samples abroad when necessary.

National alliances of patient organizations and patient representation

In Italy, UNIAMO (*Federazione Italiana Malattie Rare - FIMR*)¹⁷¹ is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 95 patient organisations representing over 600 RDs. UNIAMO publishes a newsletter and organizes 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 sometimes support specific actions.

¹⁶⁹ <http://www.liebertonline.com/doi/abs/10.1089/gtmb.2009.0097>

¹⁷⁰ Information extracted from the Orphanet database (May 2011).

¹⁷¹ <http://www.uniamo.org/>

Grants for activities of patients' organisations are coming mainly from private sponsorship, charities and income tax donations. UNIAMO's goals for 2010 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 difficult to find. Many of these drugs can be prepared in the galenic laboratories of the pharmacies in a personalised manner. "Galeno Help - Pharmacist help 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.
- "Building a Community for rare diseases" is funded by Fineco Bank. This initiative offers information paths to enable rare disease community's participation in the processes of consultation in public health matters. In particular, it is addressed to rare disease patients and their families, general practitioners, paediatricians and health professionals.
- "The Atlantis Code" is aimed at fostering the culture of research in rare diseases. Developed in partnership with the Telethon Foundation, it involves rare disease patient organisations in the attempt to identify research priorities and provide answers to the patients' needs. Three seminars were organised. The outcomes of this survey were matched up with the results of a similar investigation carried out by EURORDIS at European level.
- "Momo" intends to bring together, with a sole 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.

The ISS has 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. The *Consulta* concluded its activity in December 2010.

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, and experts on these disorders. 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.

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 Paediatric 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 team also maintains the Orphanet-Italy site¹⁷². The Orphanet portal is available in Italian.

Official information centre for rare diseases

A specific service is run by the Italian NCRD which provides information to patients, families and health professionals by means of a dedicated website and a telephone helpline. The service provides: support to health professionals and patients on centres of expertise present in the national territory; availability and elaboration of specific guidelines for clinical management of rare diseases; information on orphan drugs available in the country; collaboration with patient organisations (quality of life, access to social and health services, etc.).

Help line

The Italian National Centre for Rare Diseases (based at the ISS) runs a telephone helpline dedicated to rare diseases (800.89.69.69). The number is advertised on the ISS-NCRD web page.

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. The official website of the Ministry of Health provides information about legislative and administrative issues. Online Regional information is also available. Other services are run by patient organisations and are largely heterogeneous in their coverage.

Best practice clinical 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 documents 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.

About 40 guidelines dedicated to diagnosis, treatment and clinical management of rare diseases have been developed in 2010 by the Lombardy Region¹⁷³.

The working group of the National Committee for Bioethics (CNB) and the National Committee for Biosafety, 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.

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 University of Padua.

The NCRD organises residential courses and learning activities dedicated to the empowerment of patients, health professionals and policy makers¹⁷⁴. This program is included within the project "Rare diseases: from monitoring to training" funded by the Ministry of Health (for example, "Course on Orphan drugs and their accessibility", 28-30 January 2010 and 23 April 2010; "Course on rare diseases: from diagnosis to treatment", 20-21 October 2010). A project run by the NCRD is dealing with "Rare diseases from monitoring to training".

A major role in education of medical doctors is carried out by patient organisations (for example, UNIAMO's projects "Knowing to assist" and "Mercury", see above "National alliances of patient organisations and patient representation" section).

European National Conference

On 11-13 November 2010 UNIAMO, in collaboration with EURORDIS, organised a national conference on rare diseases in Florence in the context of the Europlan project. This conference was arranged in two plenary sessions and six thematic workshops on the following topics: methodology and governance of a national plan/strategy; definition, codification and inventorying of rare diseases; research on rare diseases; standards of care for rare diseases; centres of expertise/European reference networks; patient empowerment and specialized services; orphan drugs and accessibility to treatments. Representatives of patient organisations,

¹⁷² <http://www.orphanet-italia.it/national/IT-IT/index/homepage/>

¹⁷³ <http://malattierare.marionegri.it/content/view/111>

¹⁷⁴ <http://www.iss.it/cnrm/appu/index.php?lang=1&tipo=56&anno=2011>

researchers, funding agencies (AIFA, Telethon, Farindustria), health policy makers (Health Ministry, ISS, Regions), representatives of the major scientific societies (FISM, FIMMG, FIMP, SIP, SIGU, SIMGePeD) and the Orphanet-Italy team gathered to discuss the transferability of EUROPLAN recommendations into the Italian context and to provide advices for a national strategy. 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. The final report of the conference is available online¹⁷⁵.

National rare disease events

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. The collaboration with the National volleyball League allows, since 2008, the event to reach a broader public.

On the occasion of the 2010 Rare Disease Day, UNIAMO organised a march in Rome, *Insieme per Vincere* (Together we win), on 21 February 2010. A choral concert was also organised at the Fenice Opera House in Venice on 28 March 2010.

The event *Figli di un male minore? (Children of a lesser evil?)* was held at Valle Theatre in Rome on 25 February 2010. Panel sessions were organised with influential representatives for each thematic area. This event intended to explore the state of art in the field, to discuss important issues and to celebrate success of the rare disease community, reinforcing the awareness of the public opinion and highlighting health care priorities in Italy. This event was attended by the Italian Minister of Health.

On 27 January 2010, a conference was organised by the ISS in Rome on Genetic Testing and Quality Standardisation and Assurance. The event aimed to illustrate and discuss strategies, results and future developments of the National External Evaluation of Quality for genetic tests, coordinated by the NCRD, and to lay the basis for the promotion of the proper use of genetic tests for diagnosis and clinical practice.

On 22 February 2010, ISS organised the congress "Rare diseases and orphan drugs".

On 2 March 2010, ISS organised the second award ceremony "*Il Volo di Pegaso – Raccontare le malattie rare: parole e immagini... oltre l'ignoto*" (The flight of Pegasus – Narrating rare diseases: words and images... beyond the unknown), with the aim of raising awareness of rare diseases and their community.

On 7 May 2010, a convention on rare diseases was organised in Naples by CNR. The meeting was focused on scientific research, social problems and political initiatives.

On 23 June 2010, ISS coordinated a meeting on "Rare diseases and orphan drugs" at the annual event SANIT, organised by the Ministry of Health.

On 16 July 2010, ISS organised a conference on "Narrative medicine and rare diseases".

On 17-18 September 2010, Telethon-Italy and UNIAMO organised in Naples a meeting, *The Atlantis Code*, to promote research on rare diseases.

On 1 October 2010, a conference was held in Vicenza to discuss advances towards a national rare diseases plan (*Verso un Piano Nazionale sulle Malattie Rare*), which brought together a range of stakeholders.

On 1 October 2010, ISS organised a meeting on "Pet therapy and rare diseases".

The first National conference of Biomedical Research on 8-9 November 2010, Cernobbio, included a workshop on "Research in rare diseases". This conference intended to be an annual meeting to debate and in-depth examine the development of biomedical research in Italy, involving all stakeholders (Health Ministry, researchers, IRCCSs, ISS, research bodies and institutions, CNR, MIUR, University, pharmaceutical, medical devices and venture capital companies), in order to promote tools for partnerships and collaborations.

On 26 November 2010, ISS organised the joint congress on "Primary prevention of birth defects by folic acid" and "Registries of congenital malformations".

Other events announced in *OrphaNews Europe* included: Developmental Neurosciences and Mental Retardation Conference (29 February 2010, Rome); a workshop on Prader-Willi syndrome organised by Bambino Gesù Paediatric Hospital (10 September 2010, Rome); the 13th SIGU Conference (15 October 2010, Florence).

¹⁷⁵[http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report_italy_europlan.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf)

The NCRD also organises an annual international rare diseases meeting and several national meetings each year. Telethon-Italy arranges a fundraising event every year to promote research on genetic diseases. Every two years, Telethon-Italy organises a convention on rare diseases research, at Riva del Garda, to discuss with rare disease patient organisations and researchers the results achieved and to be achieved.

Research activities and E-Rare partnership

Research activities

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)¹⁷⁶, 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 diseases¹⁷⁷ had a total budget of €8 million. The call for projects was published in 2008 and 13 projects were granted in 2010.

AIFA issued calls to fund independent research on the development of orphan drugs. 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 drugs. Three topics were included in the clinical research area concerning rare diseases: the benefit-risk profile of orphan drugs 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 drug 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.

The annual Telethon was able to fund 36 out of the 48 selected research projects on genetic diseases thanks to fundraising activities in 2009.

Foundations and associations promote campaigns funding genetic research or research on specific diseases. Voluntary funds can be collected through general taxation.

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 will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

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.

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, EUROTRAPS, EURPIFNET, EUROSD, EPINOSTICS, ERMION, EUROGEBETA, EURORETT, EUROPSPA, EUMITOCOMBAT, EURAMY, EURAPS, EUREGENE, EURO CARE-CF, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, INHERITANCE, HAE III, HMA-IRON, HSCR, KINDLERNET, MTMPATHIES, LEISHMED, LIGHTS, MALARIA AGE EXPOSURE, MANASP, MITOCIRCLE, MOLDIAG-PACA, MCSCS, MILD-TB, MM-TB, MYELINET, MYORES, NANOMYC, NEUROKCNQPATHIES, NEUROPRION, NEURO PROMISE, NEUROSIS, NMD-CHIP, NSEURONET, OSTEOPETR, PEROXISOMES, PNSEURONET, PROTHETS, PODONET, PEMPHIGUS, RD PLATFORM, RISCA, READ-UP, SIOPEN-R-NET, SPASTICMODELS, SME MALARIA, STEM-HD, TAMAHUD, TARGETHERPES, VITAL, WHIPPLE'S DISEASE and WHIMPATH.

Italy contributes to the following European registries: EUROCAT, TREAT-NMD, HAE-registry, RBDD, AIR and EURO CARE CF. NCRD coordinates the EUROPLAN project (see section on activities at European level for further information) and a service project for the Evaluation of Neonatal Screening practices in EU Member States.

¹⁷⁶ <http://www.agenziafarmaco.gov.it/>

¹⁷⁷ http://www.quotidianosanita.it/cronache/articolo.php?&&articolo_id=1144&&cat_1=1&&cat_2=0

Orphan drugs^{178,179}

AIFA is the main body in charge of the introduction of orphan drugs onto the Italian market. The National Registry of Orphan Drugs includes data on the diagnosis and follow-up of patients treated with orphan drugs. These drugs are authorised at central level by EMA (European Medicines Agency) and reimbursed by the National Health Service. The National Registry of Orphan Drugs, established by AIFA and managed in collaboration with the 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 nationwide coverage, in other words, to address all Italian Centres qualified to distribute drugs and to prescribe orphan drugs.

Orphan drug committee

There is no specific orphan drug committee at national level in Italy.

Orphan drug incentives

AIFA has established an innovative funding scheme (*Fondo AIFA 5%*) which requires Italian pharmaceutical companies 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 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 drugs for rare diseases. At the beginning of 2009, three calls for proposals (2005-2007) had been finalised and 69 studies had received funding in the area of rare diseases.

Since 2005, orphan drug research in Italy has benefited from the "*Fondo AIFA 5%*", which also finances the compassionate use of Orphan Drugs. In 2006, for example, some 30 independent research protocols in the area of rare diseases and orphan drugs were selected for funding by AIFA through this unique initiative. In 2008, however, rare diseases and orphan drug research did not figure amongst the priority areas.

Orphan drug availability

In Italy 42 out of the 62 orphan drugs approved by EMA are marketed and their cost, for the therapeutic indication, is fully paid by the National Health System. Of the remaining 20 orphan drugs approved by EMA, 10 have a pending request at AIFA by the companies in charge of pricing and reimbursement and their assessment is ongoing, and the marketing authorisation in Italy has not been sought for the remaining 10 orphan drugs¹⁸⁰. A list of orphan drugs with European marketing authorisation and the date of their publication in the Official Gazette concerning their marketing in Italy is available¹⁸¹.

Orphan drug reimbursement policy

In Italy drugs are catalogued in A and C classes, depending on their reimbursement. Costs of A class drugs are totally paid by NHS and free of charge for citizens, while C class drugs are paid entirely by patients. Reimbursement is granted for all orphan drugs which follow the centralised marketing authorisation procedure. Moreover, for all drugs which are not currently classified in the A class, 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 the C drugs to their population. According to AIFA, the orphan drug 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 drugs was €12,981,636,953 for 21,971,349,308 DDs. Thus, the DDs cost for orphan drugs was about €100, compared to €1.60 for non-orphan drugs.

¹⁷⁸ This section has been written using information from the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp49-53).

¹⁷⁹ 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 (pp15-16)

¹⁸⁰ According to the Final Report of the Europlan National Conference, 11-13 November 2010

[http://download.eurodis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final_report_italy_europlan.pdf](http://download.eurodis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf) (p16).

¹⁸¹ http://www.iss.it/binary/orfa/cont/Farmaci_orfani_in_Italia_Feb_2009.pdf (document accessed May 2011 and last updated in February 2009).

Other initiatives to improve access to orphan drugs

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96¹⁸² (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 authorized 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 authorised¹⁸³. A Ministerial Decree of 8 May 2003¹⁸⁴ 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 Decree¹⁸⁵ 23/1998, provided that this decision is made on a named patient basis, documented evidence is provided, and no other treatment is possible.

Orphan drug pricing policy

No specific information reported.

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. At governmental level the competence belongs to the Ministry of Social Affairs. 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 and is felt to be not fully satisfactory.

1.15. LATVIA **Definition of a rare disease**

Stakeholders in Latvia accept the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10’000 individuals, although there is no official definition of rare diseases in laws and regulations.

¹⁸² 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).

¹⁸³ KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (p50)

¹⁸⁴ Ministerial Decree 8 May 2003 *Uso terapeutico di medicinale sottoposto a sperimentazione clinica* (published in GU 28 July 2003, n. 173).

¹⁸⁵ 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).

National plan/strategy for rare diseases and related actions

There is currently no national plan for rare diseases in Latvia. The costs related to rare diseases are currently included in the national health care budget. Work has recently started on a national plan. A working group including the Ministry of Health and specialists has been established with the aim of elaborating a national plan by 2013.

A National Cancer Control Programme (2009-2015) was adopted through order No.48 of the Cabinet of Ministers of the Republic of Latvia on the 29 January 2009 by the Cabinet of Ministers, included rare cancers. In August 2009 a regulation was introduced which allows for 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 the Latvian State University Children's Hospital provides genetics services.

Registries

The Centre of Health Economics 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 which 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 under the supervision of the International Society of Neonatal Screening.

Genetic testing

Genetic testing is available in Medical Genetic Clinic, Molecular Laboratory, Riga Stradins University, Scientific Laboratory and in Latvian BioMedical Research and Study Center. There are no national guidelines and specific conditions for reimbursement of expenses related to tests have not 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 database¹⁸⁶.

National alliances of patient organisations and patient representation

In 2009 the Latvian Rare Disease Organisation Caladrius¹⁸⁷ was launched on the occasion of the 2nd Rare Disease Day. The mission of the organisation is to provide patients with the relevant information and support and to represent patients. Association representatives also presented Caladrius at the Latvian Parliament *Saeima* Social and Employment Matters Committee, and a press conference was organised in Riga. In 2010 Caladrius established a fund to help rare disease patients who could not otherwise fund their treatments: the organisation had obtained public benefit organization status so as to legally collect funds for this action. In Latvia are a number of other rare disease and rare disease-related patient organisations, including the Haemophilia Society, the Society for People with Disabilities Motus Vitae. These organisations often collaborate with one another. Palidzesim.lv is a non-governmental organisation in Latvia which financially supports children and families to confirm a diagnosis of rare diseases by sending patients or medical samples abroad¹⁸⁸.

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

¹⁸⁶ Information extracted from the Orphanet database (May 2011).

¹⁸⁷ www.caladrius.lv

¹⁸⁸ www.palidzesim.lv

organisations) in their country for entry into the Orphanet database. The Ministry of Health of the Republic of Latvia has designated the Centre of Health Economics as the representative of the Republic of Latvia to participate in the Joint Action Orphanet Europe as of April 2011.

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 using a state budget.

Help line

There are non-rare disease specific help lines run by the state, some with a state budget, to help patients 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.

Best practice clinical guidelines

No best practice guidelines for rare diseases have been produced at national level in 2010.

Training and education initiatives

The Baltic Metabolic Meeting 2010 (23 -24 March 2010) included training sessions on lysosomal storage diseases.

Europlan national conference

Latvia did not hold a Europlan national conference in 2010.

National rare disease events in 2010

Events were organised to mark Rare Disease Day 2010 by the Latvian Rare Disease Organisation Caladrius.

Hosted rare disease events in 2010

The Latvian Medical Genetics Association together with Baltic Metabolic Group, "Biomarine" and "Swedish Orphan International AB" organised the Baltic Metabolic Meeting 2010 (23 -24 March 2010) at the Children's University Hospital, Riga, Latvia: the meeting focused on lysosomal storage diseases

Research activities and E-Rare partnership

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.

E-Rare

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

Participation in European projects

Latvian teams participate/ participated in the following European Reference Networks for rare diseases: Dyscerne and PAAIR. Latvian teams contribute to the following European registry: EURO CARE CF. Latvia contributes to the EUROPLAN project.

Orphan drugs

The State Agency of Medicines of Latvia is responsible for regularly collecting and distributing information on medicines, including orphan drugs, as well as collecting and compiling information on the safety, evaluating drug risks and coordinate measures of medicine use risk mitigation, according to Regulation No.1006 of the Cabinet of Ministers of December 7, 2004 "State Agency of Medicines Statutes".

Orphan drug committee

A representative of Latvia is a member of the Committee for Orphan Medicinal Products (COMP) of European Medicines Agency.

Orphan drug 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 for the treatment of a rare disease.”¹⁸⁹

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 drugs is valid in all European Union (including Latvia) and EEA-EFTA states.

Orphan drug availability

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 drugs) in a register¹⁹⁰ of medical products of the Republic of Latvia (according to Regulation No.376 of the Cabinet of Ministers of May 9, 2006 “Procedures for the Registration of Medicinal Products”).

Orphan drug reimbursement policy

12 orphan drugs are included in the Latvian national reimbursement drug lists in 2010:

- List A: Tevagrastim (filgrastim) and Omnitrope (somatropin).
- List B: Xeloda (capecitabine).
- List C: Enbrel (etanercept); Erbitux (cetuximab); Glivec (imatinib); Herceptin (trastuzumab); Hycamtin (topotecan); Mabthera (rituximab); Novoseven (human recombinant coagulation factor VIIa – eptacog alpha (activated)); Temodal (temozolomide); and Velcade (bortezomib).

Glivec has both European orphan designation and European marketing authorisation. All the other orphan drugs included in the Latvian national reimbursement drug lists have European marketing authorisation without prior orphan designation in Europe.

17 orphan drugs are reimbursed within the framework of individual reimbursement system in Latvia in 2010: Exjade, Revatio, Volibris, Avastin, Sprycel, Alimta, Votrient, Nexavar, Sutent, Atriance, Thyrogen, Cystadane, Wilzin, Humira, Keppra, Diacomit, and Rilutek.

Orphan drugs for children are available as a part of the special programme for Children’s University Hospital, Riga. Orphan drugs are partially available via the reimbursement system.

2% of reimbursement budget is intended for individual reimbursement with limitation up to 10 000 LVL/year for a single patient. Funds for the individual reimbursements cover not only expenditures of medicines for treatment of rare diseases, but also for medicines which are required for life assurance functions and not included in the positive reimbursement list.

Some orphan drugs (e.g. Imatinibum, Dasatinibum, Nilotinibum) are included in the positive reimbursement list.

Other initiatives to improve the availability of orphan drugs

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).”¹⁹¹

Orphan drug pricing policy

No specific policy is in place.

¹⁸⁹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp16-17)

¹⁹⁰ <http://www.zva.gov.lv/index.php?id=112&top=112&large=>

¹⁹¹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp16-17)

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” (Regulation 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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

There is currently no national plan/strategy for rare diseases in Lithuania and there is no budget currently dedicated to rare diseases in Lithuania. Expenses of health care services and drugs are reimbursed from Compulsory Health Insurance Fund as for other groups of patients. The Ministry of Health Decree Nr.V-239 of 31 March, 2009, established an Action Group for the development of a National Plan for Rare Diseases in Lithuania. The Ministry of Health Care is currently organising an interdisciplinary working group (including medical professionals, representatives of patient organisations, health care administrators) to develop a National plan for rare diseases.

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 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.

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 Healthcare Minister of Lithuania of 6 December 2004 “Regarding the Approval of Universal Screening of Newborns for Inborn Metabolism Disorders Procedures”).

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.

Diagnostic tests are registered as available in Lithuania for 4 genes and an estimated 3 diseases in the Orphanet database¹⁹².

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

¹⁹² Information extracted from the Orphanet database (May 2011).

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.

Official information centre on rare diseases

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

Helpline

There is currently no help line dedicated to providing information on rare diseases, but other general help lines (e.g. providing psychological support) exist.

Other sources of information on rare diseases

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.

Best practice clinical guidelines

A "National agreement for cystic fibrosis diagnostic and treatment: evidence based methodical recommendations"¹⁹³ 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.

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" was introduced for medical students.

Europlan national conference

Lithuania did not hold a Europlan national conference in 2010.

National rare disease events in 2010

To mark Rare Disease Day 2010, a seminar on "Rare hereditary childhood cancers" was held on 5 March 2010.

On 24 April, 2010, for the second time, a "DNA day in Lithuania" event was organised by the Lithuanian Society of Human Genetics. This event, commemorating the international DNA day, attracted students from all over the country. An essay competition took place involving topics proposed by the ESHG. The main goal of the competition was to expand the schoolchildren and teachers knowledge about genetics and to encourage their interest in the subject. At the end of the event, children were brought on an excursion to the Centre for Medical Genetics at Vilnius University Hospital Santariškių Klinikos and introduced to the principles of rare disease diagnostics methods.

Topics related to rare diseases and rare cancers were included in a number of national and international congresses in 2010 in Lithuania.

¹⁹³ <http://www.pediatrija.org>

Hosted rare disease events in 2010

No specific activity reported.

Research activities and E-Rare partnership**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.

E-Rare

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

Participation in European projects

Lithuanian teams participate, or have participated, in the following European Reference Networks for rare diseases: ECORN CF and PAAIR. Lithuanian teams participate, or have participated, in the EUROPEAN LEUKEMIA NET research project. Lithuania contributes to the following European registry: EUROCARE CF. Lithuania has contributed to the EUROPLAN project.

Orphan drugs**Orphan drug 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 drug incentives

No specific activity reported.

Orphan drug availability

Orphan drugs area available in the same way as the medicines authorised in all EU states. The website of the Lithuanian State Medication Control Agency¹⁹⁴ provides information including the list of authorised medicines but does not give any other information concerning orphan drugs apart from that provided by the EMA concerning orphan drugs with EU market authorisations.

Orphan drug 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 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, Healthcare Ministerial Order 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 Health Ministry's State Patient Fund, 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 Health

¹⁹⁴ <http://www.vvkt.lt/>

Ministry's State Patient Fund Directorate No 1K-149 of 22 November 2005; Official Gazette, 2005, No 139-5037)."¹⁹⁵

Other initiatives to improve access to orphan drugs

No specific activity reported.

Orphan drug pricing policy

No specific activity reported.

Orphan devices

The Committee at the Health Ministry's State Patient Fund 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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

The 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. This Task Force will soon propose 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 2011¹⁹⁶.

The results of the survey show that obtaining a diagnosis is often difficult for rare diseases patients in Luxembourg; that medical and scientific knowledge is often insufficient; that there is a lack of information, and orientation of patients as well as insufficient coordination between those treating the patient; that there are problems with the management of rare diseases and there is a lack of quality care; that there are inequalities in the access to a diagnosis, treatments and care; and that rare diseases have serious social consequences. A number of recommendations have been made on the basis of these results including: the elaboration of a national plan for rare diseases; an official definition of rare diseases; to inform and raise awareness of rare diseases; to ensure equal access to diagnosis, care the treatment; to provide specific help services for patients with rare diseases and their families; to support rare disease patient organisations and involve them in national

¹⁹⁵ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p17)

¹⁹⁶ <http://www.sante.public.lu/fr/catalogue-publications/maladies-traitements/maladies-rares/index.html>

rare disease actions; to ensure international collaboration; to help advance research; and to ensure the sustainability of rare disease initiatives at national level.

According to the results of the survey, 95% of patients with rare diseases residing in Luxembourg have sought 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.

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 will 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.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

European national conference

Luxembourg did not hold a European national conference in 2010.

National rare disease events in 2010

No specific information reported.

Hosted rare disease events in 2010

Luxembourg hosted the first meeting of the European Union Committee of Experts on Rare Diseases (9-10 December 2010) as well as a EUCERD workshop on centres of expertise and European Reference Networks for rare diseases (8-9 December 2010).

Research activities and E-Rare partnership

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.

E-Rare

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

Participation in European projects

Luxembourg does not currently participate, or has not participated, in any European Reference Networks for rare diseases. Luxembourg contributes to the following European registry: EURO CARE CF. Luxembourg contributes to the EUROPLAN project.

Orphan drugs

Orphan drug committee

The Task Force aims to create a national medical commission to consult on issues regarding access to and reimbursement of orphan drugs.

Orphan drug incentives

No specific information reported.

Orphan drug availability

No specific information reported.

Orphan drug reimbursement policy

No specific information reported.

Other initiatives to improve access to orphan drugs

No specific information reported.

Orphan drug pricing policy

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

No specific information reported.

1.18. MALTA

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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.

An estimate of about €1-2 million will be earmarked towards the implementation of actions in the field of rare diseases between 2013 and 2015.

Centres of expertise

There are currently no official reference centres of expertise for rare diseases in Malta. 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 and developed.

Registries

Malta contributes to the EUROCAT European registry.

Neonatal screening policy

Neonatal screening is available for haemoglobinopathies and hypothyroidism.

Genetic testing

Genetic studies (karyotyping and molecular genetic studies) in foetuses and neonates born with congenital malformations or rare syndromes are available. There are 3 consultant geneticists and 2 genetics laboratories in Malta, the Molecular Genetics Laboratory and Cytogenetics Laboratory. The indicated genetic tests that are not performed in house are referred to a reference centre abroad, mainly to NHS labs in the UK. Tests are offered free of charge to Maltese and other entitled individuals.

National alliances of patient organisations and patient representation

Malta does not currently have a national alliance of rare diseases patient organisations.

Sources of information on rare diseases and national help lines

Orphanet activities in Malta

The government of Malta has not designated a national Orphanet team for Malta to date.

Official information centre for rare diseases

There is no official information centre on rare diseases in Malta to date.

Help line

Although there is no official help line for rare diseases, the agency Sapport provides support by telephone to all disabled people that request it. This service is funded by the government.

Other sources of information on rare diseases

There were no further developments in the sources of information on rare diseases in 2010.

Best practice clinical guidelines

No best practice guidelines for rare diseases have been produced at national level in 2010.

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 2010

Malta was not involved in Rare Diseases Day 2010. Funds are being earmarked for Malta's participation in the upcoming Rare Diseases Day in 2012.

Hosted rare disease events in 2010

No rare disease events were hosted in Malta in 2010.

Research activities and E-Rare partnership

Research activities

Funding for research into haemoglobinopathies and other rare genetic disorders is available through various sources (including the European Structural Funds, Ithamet and the University of Malta). 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 sector¹⁹⁷”*.

E-Rare

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

Participation in European projects

Teams from Malta do not currently participate in a European Reference Network for rare diseases. Malta contributes to the following European registry: EUROCAT. Malta also contributes to the EUROPLAN project.

Orphan drugs

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 drug committee

Orphan Drugs are registered through the centralised procedure and Malta has a member on the Committee for Orphan Medicinal Products. There is no orphan drug committee in Malta to date.

Orphan drug incentives

No specific reported activity.

Orphan drug availability

To date, 35 orphan drugs are available within the National Health Scheme (see below).

Orphan drug reimbursement policy

The Exceptional Medicines Treatment Policy allows for specific provisions for the reimbursement of orphan drugs. In 2010, three orphan drugs 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 drugs are currently being reimbursed¹⁹⁸: Amifampridine, Anagrelide, 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, Nitazoxanide, Oxaliplatin, Pegvisomant, 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. In 2010, three orphan drugs were officially introduced into the Government Formulary List.

Other initiatives to improve access to orphan drugs

New initiatives to improve access to orphan drugs have been implemented in 2010. Access to orphan drugs which are not listed in the Government Formulary List for patients with rare diseases are now being considered through the Exceptional Medicines Treatment Policy. This requires the submission of a request for treatment

¹⁹⁷ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp17-18)

¹⁹⁸ Source: Directorate of Pharmaceutical Policy and Monitoring, Strategy and Sustainability Division, Ministry of Health the Elderly and Community Care (6 May 2011)

by the clinician. Following evaluation of the request, decisions are then guided by a set of criteria which must be fulfilled for approval to be given.

Compassionate use of orphan drugs is possible but no requests for such use have been approved to date. Off label use is possible at the responsibility of the prescribing physician.

In 2010, 5 new orphan drugs were approved on a Named Patient Basis under the Exceptional Medicines Treatment Policy.

Orphan drug pricing policy

With regards to reimbursement processes within the National Health Scheme, if an orphan drug 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 medicines applies. The Pricing Policy for the National Health Scheme was launched in 2010.

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*"¹⁹⁹.

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 (The Eden Foundation). Support is also available to teachers to provide inclusive education at national level and also social security benefits for those with disabilities.

1.19. THE NETHERLANDS

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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. Therefore 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 stated their intention at the Europlan National Conference on Rare Diseases (18-20 November 2010) 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.

Currently, the health care system takes care of all diseases and funding for health care services (including those for rare diseases) is provided through government funding (prenatal screening, neonatal screening, social care, orphan drugs - intramural only) and health insurance (prenatal screening, diagnostic genetic services, treatment, orphan drugs, orphan drugs, rehabilitation).

The Steering Committee on Orphan Drugs and the Forum Biotechnology and Genetics with VSOP have taken the initiative to organise a conference on 28 January 2010 on public information and expert centres; the outcomes will be used as input for a national plan.

The Dutch Organisation for Health Research and Development (ZonMw) and the Dutch Steering Committee on Orphan Drugs were responsible for the work package of the Europlan project aimed at

¹⁹⁹ http://ec.europa.eu/health/archive/ph_threats/non_com/docs/r082_en.pdf

developing the content of the Europlan recommendations including methodological guidance on how to develop comprehensive and integrated strategies for guiding and structuring all relevant actions in the field of rare diseases. In the context of the Europlan project, a National Conference on Rare Diseases was held on 18-20 November 2010 in The Hague (see section “National Rare Disease Events”).

Centres of expertise

All Dutch stakeholders support the opinion that the (follow-up) care for patients suffering from rare diseases should be concentrated in 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 inventory the 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, however, proper coordination for rare diseases on the whole is lacking, as well as an adequate funding structure. Other highly specialised care hospitals may also function as well-coordinated centres.

Other hospitals may also function as well-coordinated centres. 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. However, in general proper coordination and continuity of care for rare diseases on the whole is lacking, as well as an adequate funding structure.

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 criteria²⁰⁰.

Registries

There is no comprehensive national patient registry in the Netherlands, but many 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 drug 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 TREAT-NMD, AIR, EUROCARE CF, EPCOT and EUROCAT.

Neonatal screening policy

On 1 January 2007, an extended neonatal screening program was launched in the Netherlands, for 17 rare disorders: phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, 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 is 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 aims at identifying and evaluating all aspects deemed relevant to the implementation of a public health

²⁰⁰ This recommendation is currently discussed at the Ministry of Health, Welfare and Sport.

action in neonatal screening resulting in a report on the practices of neonatal screening for rare disorders implemented in all the Member States.

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.

Genetic testing

Genetics services in the Netherlands are funded by the health insurance through a special budget; services include genetic counseling, chromosome analysis, biochemical (enzyme) diagnostics and DNA-diagnostics. All 8 University medical centres are licenced 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 genes²⁰¹.

Diagnostic tests are reimbursed by health care insurance if an indication exists. For tests 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 2010²⁰².

National alliances of patient organisations and patient representation

VSOP (www.vsop.nl) represents more than 60 member organisations and acts as the national alliance of rare disease patient organisations in the Netherlands, especially in the field of research, prevention, treatment and ethics. VSOP also deals with societal issues in these fields. Several more common disorders are also represented in the VSOP membership. Other umbrella organisations deal with other issues that are relevant for 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).

A specific part of the Ministry of Health's budget (CIBG - Fonds PGO) subsidises all national patient organisations with a minimum of €30,000 (maximum €90,000) per year. Patient organisations can also apply for specific project funding. In this way, VSOP's project proposal was granted (€3 million) to work on the themes of standards of care, centres of expertise and research from 2009 to 2014. Amongst others, about 17 standards of care guidelines will be developed, alongside 33 treatment guidelines for general practitioners. Both subsidy programs will probably subject to major governmental budget constraints by 2012.

The Dutch Steering Committee has organised two workshops in April and November 2010 with the aim to strengthen the voice of patients with a rare disease, in particular protecting the interests of rare disease patients.

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.

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

²⁰¹ A list is available on the website www.DNA-diagnostiek.nl.

²⁰² www.vumc.nl/cftest offers CF carrier testing for 150€

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

The Steering Committee on Orphan Drugs functions as an information centre for rare diseases and orphan drugs in the Netherlands. The secretariat of the steering committee answers various questions from pharmacists, medical specialists, patients and their families and pharmaceutical companies about rare diseases and orphan drugs. Furthermore, the Steering Committee has a signalling function in response to problems that are reported to the steering committee. Their website www.orphandrugs.nl provides general information.

Help line

General help lines are available, such as the ERFO line for information on hereditary diseases and pregnancy, which is now independent from VSOP after having been created under its auspices. Meldpunt (Information Desk from the Dutch Consumer and Patient Federation) is another general health line for information concerning social services and health care insurance.

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 issues²⁰³. The Erfocentrum also launched a new website www.erfelijkheidinbeeld.nl in 2010 on the occasion of Rare Disease Day: this website 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.

The VSOP also functions as a centre providing expertise and advocacy for patients with a rare 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 Environment, both for the general public, parents and physicians (www.rivm.nl/pns/hielprik).

Best practice clinical guidelines

Currently VSOP, in collaboration with disease specific organisations, develops guidelines for general practitioners on rare diseases, works on the realisation of standards of care and on centres of expertise and research: 17 standards of care and 33 treatment guidelines for general practitioners are currently being developed.

Training and education initiatives

In the VSOP project "The patient as an information carrier" 30 brochures are being developed on treatment and counseling of people with a rare disorder by the general practitioner (16 brochures are finished). This is carried out in close collaboration with the patient organisations and the Dutch College of General Practitioners (NHG). VSOP is currently developing courses in the field of national and European rare disease policy.

2010 the Boerhaave Committee organised 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 drugs.

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 website²⁰⁴.

²⁰³ These sites provide further web based information: www.biomedisch.nl; www.zwangernu.nl; www.zwangerwijzer.nl; www.slikeerstfoliumzuur.nl; www.prenatalescreening.nl

²⁰⁴ For instance information for screeners and information on the diseases screened: www.rivm.nl/pns/hielprik/films.

European national conference

On November 18-20 2010, patient organisations, health insurers, health professionals, politicians, policy makers, researchers and industry came together in The Hague for the National Conference on Rare Diseases, organised by the VSOP in collaboration with the Europlan project, to discuss and hopefully improve the situation of people with rare conditions. The meeting focused on four issues regarding the position of rare diseases in the Netherlands, namely: the problems recognising and correctly diagnosing rare diseases, a situation which leads to uncertainty for patients and family and often irreversible health damage; insufficient coordination of care and the fragmentation of knowledge about rare diseases; the lack of collaboration between health professionals and researchers, and lack of referrals from GPs and specialists; the absence of rare diseases on the agenda of politics and health policy, and the role of patients in this process.

For all these issues, participants formulated joint recommendations relevant to the National Plan for Rare Diseases. One key observation was that rare diseases are not considered to be a Dutch health problem, which participants agreed is a misapprehension, because of both the suffering that these diseases entail and the size of (sometimes avoidable) health care costs. Finally, it was noted in the conclusions that, unfortunately, the National Plan for Rare Diseases seems to be a low priority for the new government, other politicians and policy makers. The final report is now available online²⁰⁵.

National rare disease events in 2010

The Rare Disease Day event was organised in the Netherlands on 26 February 2010 in Oegstgeest²⁰⁶: the theme of this day was "Inspiration and action" and the event was organised by the Zeldzame Ziekten Fonds (Rare Disease Fund²⁰⁷), and the umbrella patient organization for rare diseases VSOP²⁰⁸, Steering Committee on Orphan Drugs²⁰⁹) and the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (Royal Dutch Association for the Advancement of Pharmacy KNMP²¹⁰). The Rare Disease Day started with a plenary session, during which the development of social networks from the 1950s to the present day was presented and the audience was encouraged to sign up to the creation of a new national network on rare diseases. More than half of the attendees have indicated they want to contribute to this national network, which will help draw attention to the field of rare diseases in the Netherlands and promote related actions. Furthermore, the Erfocentrum launched a new website www.erfelijkheidinbeeld.nl during the day (see section "Sources of information on rare diseases"). The organisers also announced the winner of the "Rare Angel Award" awarded to a person who has dedicated themselves to rare diseases. Frits Lekkerkerker, chairman of the steering committee orphan drugs, presented the award to the Kees Waas who has been working for years as a volunteer for people with immune deficiencies and he works on improvement of awareness for this largely unknown complex group of diseases, both in the Netherlands and at European level. After the plenary programme participants were able to meet each other and visit the "information market" set up by different patient associations, foundations and organisations that work to raise awareness of rare diseases and offer support. The Orphanet Netherlands team also had a stand and the team informed visitors about the Orphanet website, showed them how the portal works and gave out information on how Orphanet can be of use to enlarge the visibility of their organisation in Europe.

In addition to these events a range of other meetings and symposia took place in the Netherlands at national level in 2010. A symposium was organised by the Steering Committee Orphan Drugs on the theme "Orphan Drugs: from research bench to access for rare disease patients" (3 February 2010, Utrecht). The Dutch Society of Human Genetics (NVHG) organised its annual symposium on the theme "Therapy of genetic diseases" in Amsterdam (23 April 2010, Amsterdam). A meeting of the "Rare Diseases Network" was held on the 18th May 2010 in Driebergen to follow up on the actions of the 2010 Rare Disease Day and further efforts in the field of rare diseases. On 9 December 2010, the five priority medicines research programmes²¹¹ of the ZonMw (one of which is a programme on priority medicines for rare disorders and orphan drugs) which were created following the publication of the WHO report "Priority Medicines for Europe and the World", met in Amsterdam so as to stimulate networking between policy makers, researchers and representatives of funding agencies.

²⁰⁵ [http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report netherlands %20europlan.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_netherlands_%20europlan.pdf)

²⁰⁶ www.zeldzameziektendag.nl

²⁰⁷ www.zzf.nl

²⁰⁸ www.VSOP.nl

²⁰⁹ www.weesgeneesmiddelen.nl

²¹⁰ www.knmp.nl

²¹¹ <http://www.zonmw.nl/prioritymedicines>

Hosted rare disease events in 2010

Amongst the rare disease events hosted by the Netherlands in 2010 and announced in *OrphaNews Europe* were: EuroBoNeT Course on practical clinical, radiological and pathological diagnosis of skeletal tumours (14-16 February, Leiden).

Research activities and E-Rare partnership²¹²

Research activities

The preparations for executing the ZonMw programme on priority medicines for rare disorders and orphan drugs started in 2011. The main objective of this to stimulate translational research in rare diseases with the aim of developing therapies. For the programme €13.6million is available. The first call will be 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). The Steering Committee on Orphan Drugs funds some rare disease projects (max. €50,000 per year).

Another programme specific to orphan drugs (STIGON-Weesgeneesmiddelen) ended in 2010 and involved two projects with a total budget of €500,000: the appointment of an orphan product developer (see below) and of a PhD student. The PhD student defended this thesis "From research on rare diseases to new orphan drug development" on 3 February 2010. His research (e.g. on analysis of factors in the success or failure in orphan drug development) resulted in several papers in international peer-reviewed journals. .

There are tax reductions for R&D in high-tech start-ups (named the "WBSO measure") from which orphan drug 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 drug companies can benefit from.

The Netherlands Organisation for Scientific Research bequeathed €22.5 million 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.

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 will not participate in the 3rd E-Rare Joint Transnational Call (2011).

Participation in European projects

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). 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, EURO CARE-CF, EURO GENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, EVI-GENORET, EUROSD, EUROPADNET, EUROSTEC, HSCR, GENESKIN, GEN2PHEN, GENTECH, HDLOMICS, IMMUNOPRION, MLC-TEAM, NEMMYOP, NSEuroNet, NEUROSI, 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. The Netherlands contributes to the following European registries: TREAT-NMD, AIR, EURO CARE CF, EPCOT and EUROCAT. The Netherlands contributes to the EUROPLAN project.

²¹² This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp53-62).

Orphan drugs^{213,214}***Orphan drug committee***

The Steering Committee on Orphan Drugs (Stuurgroep WGM) was established in 2001 by the Minister of Health: its mission is to encourage the development of orphan drugs and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases. This committee is 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 is involved in the EC projects E-Rare, Europlan and Polka. The action plan for this committee for 2008-2011 covers three priority areas: 1) improved access to health care and treatment through centres of expertise, 2) the stimulation of research and development of Orphan Drugs, 3) the creation of a sustainable reimbursement system. The budget of this committee is €450,000 per year. The Steering Committee will not be funded by the Dutch government after 2011 and will no longer exist as a governmental committee. In 2011 the steering committee will focus on the draft for a national plan in close cooperation with different stakeholders.

Orphan drug incentives

In 2006 an orphan product developer was appointed within the Dutch Organisation for Health Research (ZonMw) and development to stimulate Dutch academic researchers and pharmaceutical industries to develop orphan drugs. This project (as part of the STIGON-Weegeeneesmiddelen programme) ended in 2010 and was paid for by the Ministry of Health over more than four years. A project has started at the end of 2010 to elaborate whether this post should be handed to the Dutch Medicines Evaluation Board or an industry platform.

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 is available from the Dutch Steering Committee on Orphan Drugs. In the case of orphan medicinal products for a rare disease for which no alternative treatments exist, there is no obligation for companies to show pharmaco-economic data. In individual cases this may also be the case for orphan medicinal products for a disease with a prevalence of less than 5:10,000 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 Orphan Drugs and is executed by the Netherlands Organisation for Health Research and Development (ZonMw). This initiative will help stimulate the development of orphan drugs 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 drug development. The scheme will run from January 2009 to the end of November 2011 with a total budget of €180,000. 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. The first ODD-support grant has been awarded to enterprise DNage for its product Prodarsan, currently under development for the treatment of Cockayne syndrome. A second ODD-support subsidy was awarded to to-BBB technologies for glutathionepegylated liposomal doxorubicine hydrochloride (2B3-101), being developed as a treatment for brain cancer including glioma. In a press release in summer 2010, Remco de Vruueh, Orphan Product Developer for the Dutch Steering Committee observed that "Both products are prime examples of a number of novel innovative medicinal products that are currently being developed by the small and medium-sized bio-pharmaceutical industry in the Netherlands, many of which are directed to rare, but life-threatening or chronically debilitating disorders". At the end of 2010 the third ODD-support grant has been awarded to the

²¹³ This section has been written using KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp53-62)

²¹⁴ 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) (pp21-23)

Dutch subsidiary office of Taiwan Liposome Company for its product Lipotecan, currently under development for the treatment of hepatocellular carcinoma.

Orphan drug availability

In 2010, 58 Orphan Drugs were available the Netherlands.

Orphan drug reimbursement policy

In the Netherlands the following orphan drugs are reimbursed: Afinitor, Aldurazyme, Carbaglu, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Glivec, Ilaris, Increlex, Kuvan, Lysodren, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Prialt, Replagal, Revatio, Revlimid, Revolade, Siklos, Soliris, Somavert, Sprycel, Tasigna, Thelin, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Yondelis, Zavesca.

An application for reimbursement is in procedure for Arzerra, Cayston, Ceplene, Firdapse and Inovelon. In the mean time the products are available when ordered by a physician or a pharmacist.

The following orphan drugs are available when ordered by a physician or a pharmacist either through a hospital budget or on a named-patient basis: Atriance, Busilvex, Firazyf, Gliolan, Litak, Mepact, Mozobil, Pedeia, Photobarr, Rilonacep Regeneron, Savene, Tepadina, Trisenox and VPRIV.

For the use of orphan drugs in university hospitals, a reimbursement method ("*beleidsregel weesgeneesmiddelen*") was introduced from 1 January 2006, to increase the use of orphan drugs for treating rare diseases. The costs of the orphan drugs 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 drugs 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 drugs

There is no specific policy for compassionate use for orphan drugs but there is a general policy for compassionate use of all drugs. Off-label procedures are also the same for orphan and non-orphan drugs, and is accepted if there is evidence for the rational prescription of a medicinal product. The physician is obliged to inform the patient about all the pros and cons of the treatment and that it concerns an off-label medicinal product.

Orphan drug pricing policy

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

Orphan devices

There are no initiatives in place up to 2010 to improve access to 'orphan devices'.

Specialised social services

Most respite care services are imbedded in the general health care system: 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 of a prevalence of no more than 5 in 10,000 individuals is widely used amongst stakeholders. In Poland this equates to less than 19,000 patients.

Diseases with less than 750 patients are considered in Poland to be 'ultra-rare'. This definition was introduced in the Order of the President of the National Health Fund on rules regarding introduction of therapeutic health programmes in 2007. In case of diseases considered as 'ultra-rare' it was possible to bypass the cost-effectiveness assessment of such programme. Since the reimbursement system has changed (in particular the Minister of Health is responsible for introducing new therapeutic programmes) the definition has no practical significance at the moment.

National plan/strategy for rare diseases and related actions

No national plan or strategy for rare diseases exists at the moment in Poland. Rare diseases are neither mentioned in the National Health Programme 2007-2015, nor in the Strategy for the Development of Science in Poland up until 2015. There is no dedicated budget for rare diseases.

The Rare Disease Team was established by way of the 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 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 suggestions on rare diseases policy and reimbursement of orphan drugs. In the result of the Team's works several orphan drugs for ultra-rare diseases were included in health programmes (administered free of charge to patients).

During the 5th European Conference on Rare Diseases in Krakow (13-15 May 2010) several patient organisations and health professionals signed the petition to the Polish Minister of Health requesting the government to initiate the works on the Polish National Plan for rare diseases.

A National Conference on Rare Diseases was organised by the Polish Cystic Fibrosis Foundation MATIO and National Forum for the Therapy of Rare Diseases on 22 October 2010 in Krakow in the context of the Europlan project to discuss a broad European strategy for rare diseases and the recommendations of Europlan (see section "National rare disease events").

At the first meeting of the newly-elected Commission of Systemic Diseases, a working group of Poland's paediatric scientific committee (the Committee of Human Development) working within the framework of the independent government-funded research organisation the Polish Academy of Sciences, it was decided to focus on rare disease issues. Rare diseases will be included in the Committee of Human Development working programme over a coming four-year period. The first action toward this goal is the appointment of an Orphanet Advisory Board to the Committee in cooperation with the Polish Paediatric Society.

In addition to this, the National Program to Combat Cancers is a measure which covers all cancers, including rare cancers.

To separate the debate on national plan and the inclusion of patients in created health programmes (drugs are administered only to a limited number of patients who meet specific health criteria and were not excluded from the programme) the President of the National Health Fund established a Coordination Team for "Ultra-rare" Diseases: Its task is to qualify patients as eligible for enzyme replacement therapy in the following diseases: Gaucher disease, Pompe disease, MPS types I, II and VI.

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.

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 TREAT-NMD, EURO CARE CF, EUROWILSON, EUROGLYCAN 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 21 metabolic disorders diagnosed by gas chromatography-mass spectrometry are available in some regions through a Ministry of Health financed pilot programme.

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 153 genes and an estimated 174 diseases in the Orphanet database²¹⁵.

National alliances of patient organisations and patient representation

Although there is currently no national alliance for rare disease patient organisations in Poland, there exist a few different organisations which currently group together different rare disease patient organisations. During the Rare Diseases Conference and Europlan Conference in Krakow many patient organisations expressed the need to strengthen the cooperation of rare disease patient organisations at national level.

The Ministry of Health attempts to support a single unanimous vote of patient organisations. One patient organisations representative will be a member of the Rare Disease Team. To ensure a single voice of patients the Ministry of Health plans to facilitate discussions between their organisations in a non-formal forum created by the leader of the Rare Diseases Team.

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 their country for entry into the Orphanet database. The team also maintains a national Orphanet entry point in Polish.

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.

Best practice clinical guidelines

No specific activity currently reported.

²¹⁵ Information extracted from the Orphanet database (May 2011).

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 in Warsaw, which have been organised on a regular basis for 3 years now, as a part of the Dyscerne project. 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.).

Europlan national conference

A National Conference on Rare Diseases²¹⁶ was organised by the MATIO Foundation and the National Forum for the Therapy of Rare Diseases on 22 October 2010 in Krakow in the context of the Europlan project to discuss a broad European strategy for rare diseases and the recommendations of Europlan. Participants included medical professionals, policy makers and patient organisations. The following themes were discussed: managing and monitoring a national plan for rare diseases; definition, codification and registration of rare diseases and dissemination of information and training; research and clinical trials in the field of rare diseases; standards of care in the treatment of rare diseases, specialised centers and orphan drugs; support of initiatives and activities for patients; ensuring sustainable development; and the collection of expertise at European level. The final conference report is available online²¹⁷.

National rare disease events in 2010

To mark Rare Disease Day 2010, a meeting at the Warsaw Children's Memorial Health Institute was organised on 2 February 2010 which was attended by around 80 participants and a one-day conference was organised in Warsaw on 25 February 2010 for teachers, educators, psychologists and parents. Several TV programmes were broadcast and publications appeared in the press on the theme of Rare Disease Day 2010 in addition to a press conference on 22 February 2010.

On 20 February 2010 the Society of the patients with Niemann-Pick and related diseases organised a one-day conference for patients, families and professionals in Warsaw, with invited speakers from the Mayo Clinic and Rostock Medical University. The 9th Polish National Cystic Fibrosis Week (22-28 February 2010) was organised to coincide with Rare Disease Day 2010 by the MATIO Foundation²¹⁸.

Hosted rare disease events in 2010

The 5th European Conference on Rare Diseases took place in Krakow (13-15 May 2010). A number of satellite meetings were also organised by Europlan, Eurordis and Orphanet. The theme of the conference was "From policy to effective services for patients": the conference concentrated on national plans and strategies for rare diseases, European reference networks and centres of expertise, information and medical education, science from bench to bedside, and rare diseases in central and Eastern Europe, amongst other topics.

Research activities and E-Rare partnership

Research activities

There are no research programmes 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. .

E-Rare

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

Participation in European projects

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, Care-NMD and TB PAN-NET. 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

²¹⁶ <http://www.europlan.org.pl/>

²¹⁷ http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_poland_europlan.pdf

²¹⁸ http://www.cfww.org/cfe/article/1112/IX_National_Week_of_Cystic_Fibrosis

PLATFORM and SIOPEN-R-NET. Polish teams contribute to the following European registries: ERCUSYN, RARECARE, SCNIR, TREAT-NMD, EUROCARE CF and EUROCAT. Poland contributed to the EUROPLAN project.

Orphan drugs

Orphan drug committee

There is currently no orphan drug committee in Poland. For details please refer to the part on national plans.

Orphan drug incentives

No specific activity reported.

Orphan drug availability

No specific information on availability of orphan drugs (i.e. number of orphan drugs commercialised in Poland) has been provided. Information on reimbursement procedures is detailed below.

Orphan drug 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, 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 authorization 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 health programmes (e.g. Crohn disease, Prader-Willy syndrome, cystic fibrosis). Of these, 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. Thus late on-set Pompe patients do not qualify for the therapy reimbursement.

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 access to orphan drugs

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. If a company donates a drug, it is subject to taxation, which further limits potential compassionate use.

Orphan drug pricing policy

No specific activity currently reported.

Orphan devices

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

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

Most stakeholders in Portugal accept the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10,000 individuals, a definition which has been adopted by the national plan for rare diseases.

National plan/strategy for rare diseases and related actions

On 12 November, 2008, the Portuguese Minister of Health approved a national plan for rare diseases for Portugal. The plan adheres closely to the structure outlined during the European Conference on Rare Diseases, which took place in Lisbon in 2007. The “*Programa Nacional de Doenças Raras*”, which has already undergone a period of public consultation, delineates two general and seven specific objectives and was supposed to have been implemented within an initial timeframe running from 2008-2010, followed by a consolidation period stretching from 2010 to 2015.

The main objectives are the creation and improvement of national measures in order to satisfy the necessities of people with rare diseases and their families vis-à-vis medical services and care, and the improvement of the quality and equity of the provided health care measures to people with rare diseases. The objectives will be achieved by creating reference centres for rare diseases, improving the access of rare disease patients to adequate care, improving knowledge on rare diseases, promoting innovations in the treatment of rare diseases and accessibility to orphan drugs, and by assuring cooperation on national and international levels, including the countries from the EU and countries using Portuguese as their official language.

The specifics of the plan include in total 30 intervention strategies, 9 education and training strategies, and 8 strategies for data collection and information analysis. The plan also details 15 actions for evaluation. The Minister has chosen a coordinator and a national commission to oversee and put into action the various elements of the plan. This plan will cover all rare diseases: however, rare cancers are covered separately by a rare cancer plan. The budget for the kick-off year (2009) of the rare disease plan is €150,000, mostly dedicated to preparatory studies and the preparation of activities.

The national parliament approved a recommendation concerning the (priority) access to health care for people with rare diseases, in May 2009. A National Board for Rare Diseases (CNRD) was formed and its first meeting was held to prepare the plan (29 May 2009). A Coordinator for the National Plan and a National Commission were chosen by the Minister to oversee and put into action the various elements of the plan which ran from 2008-2010, followed by a consolidation period which will stretch from 2010-2015. An action plan for 2009 and 2010 was drafted, which includes the autonomous regions of the Azores and Madeira. The main priority was the implementation of a national network of reference centres for rare diseases and the implementation of a Rare Disease Patient Identification Card to facilitate access to emergency care for patients with rare diseases. In 2010, the Health Quality Department of the Directorate-General of Health (DGS) has initiated an expert working group towards the creation of Rare Disease Cards (including representatives of the two Portuguese patient alliances for rare diseases, the Portuguese Social Security Ministry and the coordinator of the National Plan. The consensus document was approved by the Ministry of Health in January 2011 and is prepared to be implemented.

With the funding of the Directorate General of Health, some projects concerning rare diseases were implemented in 2009. Unfortunately, not much has been accomplished until now within the specified objectives of the “*Programa Nacional de Doenças Raras*”. The first meeting of the implementation of National Plan on Rare Diseases was held on 25 January 2010 in order to schedule specific activities and the construct a work plan.

Centres of expertise

There are no officially designated centres of expertise for rare diseases in Portugal at the moment. However, The National Plan for Rare Diseases will support the creation of officially recognised ‘reference centres’.

In April 2010, a document on a network of national ‘reference centres’ was produced and published (“*Rede Nacional de Centros de Referência para Doenças Raras*”). The main goal of this network of ‘reference centers’ is to improve the diagnosis, treatment, information and support to patients with rare diseases and their relatives. Specialised centres within the public health system that have developed clinical activities in a rare disease or group of rare diseases throughout the years, are encouraged to apply, either by themselves or in articulation with other services, to be recognised as “reference centres”. In the summer of 2010 the document was open to public discussion, and received significant input from professionals and stakeholders. The major criticisms from the Board of the Medical Genetics College (National Medical Association, “Ordem

dos Médicos”), and of the team of Orphanet Portugal concerned the fact that the Central Administration of the Health System (ACSS) imposed a model based on the ‘centres of excellence’ already existing in other health areas, with no specific funding and which are exclusively hospital-based (although these centres can network with university, research, and private institutions, they must be based within the national health system). The Ministry of Health will approve the regulations for the choice of the national ‘reference centres’ in 2011, and the National Health Directorate (Direcção-Geral da Saúde) will then prepare the implementation process.

Following legislation establishing norms for access to therapies for enzymatic diseases, the National Institute of Health created a national network of treatment centres for these diseases: this programme cost €35 million in 2008. A list of enzymatic diseases benefiting from treatment free of charge in public hospitals is available. The same model is applied to the growth hormone therapy for some rare diseases; the list will be updated in 2011.

Registries

The National Institute of Health is creating a retrospective “historical” register for patients with the Portuguese type of familial amyloidosis. Many hospitals and private centres have patient databases (especially Medical Genetics Services and Laboratories), but these databases are not networked.

Portugal has 5 regional oncologic registries, and 3 national registries: primary immunodeficiencies, adrenal and pituitary tumours. A national registry for neuroendocrine tumours is been set in place.

Many patients are included in international registries or initiatives, of which “REGISTRY” from the European Huntington Disease Network is a good example. Portugal also contributes to the TREAT-NMD, EUROCARE CF, EUROCAT, EBAR, SCNIR, CHS, SPATAX and Euro-Wilson European registries and networks.

Though there is no global rare diseases registry in Portugal, two recent initiatives, however, may be on their way.

On 9 February 2010, the Portuguese Federation of Rare Diseases (FEDRA) presented the protocol for the Prospective Observational Study to evaluate the incidence and prevalence and characterise some rare diseases: this event was held in conjunction with the 2010 International Rare Disease Day.

The study group for rare disorders of the Portuguese Society of Internal Medicine is planning a National Registry of Rare Diseases. Discussion is still going if the registry would be for all rare diseases, though not including rare cancers, or if will include only some diseases or disease groups (such as mitochondrial disorders, haemochromatosis and others).

Neonatal screening policy

Neonatal screening for 25 diseases is available at one laboratory, at the National Institute of Health (Porto), with 10 corresponding treatment centres in main hospitals. Amongst all the diseases screened, are hypothyroidism, 9 amino acids disorders including phenylketonuria, 7 organic acidurias and 8 disorders of the β oxidation of the mitochondria.

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 272 genes and an estimated 290 diseases in the Orphanet database²¹⁹. Genetic tests are carried out by the Instituto Nacional de Saúde²²⁰ (Dr. Ricardo Jorge), as well in the laboratories located of the five medical genetics services in public hospitals, and 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 genetic testing performed in the country. When is necessary to have a test that is not done by a laboratory in Portugal, there is a formal procedure to do that exam 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 by Law 12/2005, of 26 January 2005.

This Law defines genetic information as the health information linked to 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 pedigree information.

²¹⁹ Information extracted from the Orphanet database (May 2011).

²²⁰ <http://www.insa.pt/sites/INSA/Portugues/AreasCientificas/Genetica/Paginas/LaboratorioDeReferencia.aspx>

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, excluding pre-symptomatic or 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, susceptibility, prenatal, pre-implantation forensic and identity testing can only be registered in records of genetic services that keep separate files (and these cannot be accessed by other professionals of the same or of other health institutions).

Diagnostic or pharmacogenetic testing should follow the general principles of all other health care intervention. Carrier, pre-symptomatic and 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. 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 screening, the rights of the population or groups of the population should also be protected, in addition to the individual rights.

Collection, conservation and usage of biological samples for genetic testing should be subject to informed consent separate for health care and biomedical research, including 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 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 should 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 then.

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 rare diseases alliances: FEDRA (*Federação Portuguesa de Doenças Raras*) and the Aliança Portuguesa de Associações de Doenças Raras.

FEDRA is a national alliance of several rare disease patient organisations in Portugal. During 2009, FEDRA defined their action plan in the short, medium and long term. Working groups have been established in a number of priority areas and a Scientific Council has been established. In 2010, FEDRA started a *Prospective Observational Study for Construction of a Registry of Patients with Rare Diseases*, which will last for four years

which aimed: to investigate the social and economic reality of patients with rare, chronic and disabling diseases; to determine whether the patients know about their social rights and how they use these rights; and to determine patients' knowledge of their medical history and their ability to assess the implications of the disease on their social life and the consequent integration in society. Another of FEDRA's priorities for 2010 was a wider distribution of the free FEDRA newsletter which deals with issues concerning the rights of rare diseases patients, the work done by affiliated patient organisations and scientific news.

The "Aliança" (Portuguese Alliance of Rare Disease Associations) was officially founded in 2009 and since then has developed several activities with the aim of improve Portuguese health policy in the field of rare diseases, and to create awareness to this problem. During 2010, they have launched an educational program, which was recognized by the Portuguese Ministry of Education as very valuable and important to help children understand rare diseases and integrate children with rare diseases in schools and into our society in general. This project was called "Raras com Sentido: Informar sem Dramatizar" (Rare Diseases with Sense: Inform without Drama).

FEDRA and "Aliança" participate in the committee for patients' and families' needs at the Directorate General of Health along with representatives of the Ministry of Health and the Ministry of Social Security. Patient organisations were involved in the public discussion of the rare disease plan and a project has been launched by the National Board for Rare Diseases (CNRD) to organise regular discussions with patient organisations, especially to incorporate the needs of the patients into the Portuguese Program, which was responsible for the creation of the Rare Disease Patient Identification Card.

Some Portuguese patient organisations receive financial support from the state, and there are some programmes sponsoring specific activities proposed by patient organisations. In 2008, the Ministry of Health launched calls for projects for rare disease patient organisations with a funding allocation of around €500,000. The Health Directorate has an organic 'civil society unit' that supports patient organisations and their projects.

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. This team was designated as the official Orphanet team for Portugal 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 worked in 2010 towards the relaunch of Portuguese version of Orphanet at the end of February 2011.. The Orphanet-Portugal team also created and maintains the Orphanet country site for Portugal²²¹. A national Scientific Advisory Board was formed in 2010.

Orphanet is referenced in the National Plan 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.

On 6 June 2010, plans were discussed for co-funding of Orphanet Portugal's local activities through periodical grant calls from the D.G. Saúde, together with possible partnerships with the National Plan for Rare Diseases. In October 2010, a grant proposal was submitted and is still waiting the publication of the results. It was decided that an official event, with media coverage, would be planned to announce the launch of the Orphanet website in Portuguese, as well as the constitution of the new Scientific Advisory Board. This took place on 25 February 2011, during the conference "Raros mas Iguais" ("Rare but Equal") organised by the Aliança.

The Ministry of Health has also recognized Orphanet-Portugal as the official source of information on rare diseases and orphan drugs in Portugal.

Orphanet-Portugal has established several partnerships²²² with the Centre for Social Studies, at the University of Coimbra (to update a validated the list of Portuguese patient associations); with CEIC (the National Ethics Committee for Clinical Research) and INFARMED (for updating information on approved clinical trials in the context of rare diseases and of orphan drugs in the country); with FCT (Fundação para a Ciência e Tecnologia) and FCG (Fundação Calouste Gulbenkian) for updating lists of ongoing research projects in Portugal in the field of rare diseases.

²²² An updated list of all partnerships can be consulted at www.orpha.net/national/PT-PT/index/parcerias.

²²² An updated list of all partnerships can be consulted at www.orpha.net/national/PT-PT/index/parcerias.

Official information centre for rare diseases

With funding from the Directorate General of Health (DGS), a call centre and resources centre for rare diseases was scheduled to be implemented in 2009, but is still under development.

Help line

With funding from the Directorate General of Health, a call centre was scheduled to be implemented in 2009 (see above). The patient organisation Raríssimas received funding from the Health Directorate in 2008 to prepare a rare disease help-line, the “linha rara” (www.linharara.pt) is now in place.

The Portuguese Haemophilia Association also provides some support by phone. Several other patient associations have a helpline or provide help online or by email.

Other sources of information on rare diseases

Several patient associations and medical genetics services and centres maintain online information about the diseases with which they are mainly concerned.

FEDRA organised the launch, on 23 February 2010 in Porto, of their book “Doenças Raras de A a Z, vol II”. The book has information on 41 rare diseases, with multiple mentions of Orphanet as the reference for further information concerning rare diseases. The first volume was launched in 2009.

Best practice clinical 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, a EU-funded Network of Excellence, which has developed guidelines and supports the accreditation and/or certification of genetic services, 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 Testing (www.oecd.org/dataoecd/43/6/38839788.pdf), led the process of defining the EMQN BP Guidelines for the Molecular Genetic Testing in the SCAs (dominant ataxias) (www.eurogentest.org/uploads/1283847353000/SCABestPracticeGuidelines-WebsiteVersion.pdf), and collaborated for the EMQN BP Guidelines for Molecular Genetic Testing of Huntington Disease (still being finalized).

Training and education

There is no formal programme in this area, but some medicine faculties have lectures on rare diseases, and much work is done in secondary schools and by patient organisations and health services.

In September 2009 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 Medical Genetics specialty for physicians had been recognised in 1998, the Portuguese College of Medical Genetics was formed in 1999 and the medical genetics residency (5 years training) began in 2000; the first formally, fully-trained specialists in the country finished their training in 2005.

During 2010, Aliança launched an educational program to help children understand rare diseases and also to integrate children with rare diseases in schools and in general into our society called “Raras com Sentido: Informar sem Dramatizar” (Rare Diseases with Sense: Inform without Drama). The programme was recognised by the Portuguese Ministry of Education as valuable.

Europian national conference

Portugal did not hold a Europlan national conference in 2010.

National rare disease events in 2010

Two major events took place in the context of the celebration of the Rare Disease Day 2010. FEDRA organised a day conference in Lisbon, at the Gulbenkian Foundation in the presence of Health General Director representing the Minister of Health and the president of the National Plan for Rare Diseases. Aliança organised a conference in Porto, together with Orphanet Portugal, where the national Scientific Advisory Board of Orphanet and the Portuguese Orphanet website were presented, together with the launch of the Portuguese version of the Orphanet portal, in the presence of the Portuguese Ministry of Health, the State Secretary of Health and the Director of INFARMED (National Authority of Medicines and Health Products). Both events had a significant media coverage, as reported in OrphaNews.

In 2010, Aliança launched the educational program “Raras com Sentido: Informar sem Dramatizar” (Rare Diseases with Sense: Inform without Drama). This program was launched during an event that included a pilot session of the program. This event took place on a school, having large media coverage and the presence of several key opinion leaders, stakeholders and well known people from several areas including politics, television and sports.

Aliança has also supported an event held in a Lisbon high school, organised by its final year students, in order to draw public attention to the rare disease issue and, when asked to do so, delivered info and participated on other school projects and events. Several other patient organisations associations organised local events.

Amongst other national events were the meeting of the Portuguese Association of Huntington Disease (APDH) (6 February 2010, Porto); the 14th Annual meeting of the Portuguese Society of Human Genetics (18-20 November 2010, Coimbra).

Hosted rare disease events in 2010

Amongst the hosted rare disease events that took place in Portugal and that were announced in *OrphaNews Europe* were: ISDN 2010 - 18th Biennial Meeting of the International Society for Developmental Neuroscience (6-9 June 2010, Estoril); 23rd European Conference of the European Haemophilia Consortium (22-24 October 2010, Lisbon); Eighth European Cytogenetics Conference (2-5 July 2011, Porto), ESH-EHA Conference: Innovative Therapies for Red Cell and Iron Related Disorders (16-18 April 2010, Cascais).

Research activities and E-Rare partnership

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.

E-Rare

Portugal, 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.

Participation in European projects

Portugal participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA NEUROPED and TAG. Portugal participates, or has participated, in European rare disease research projects including: CLINIGENE, EPOKS, EHDN (European Huntington Disease Network), Euro-WILSON, SPATAX, EURAMY, EURO CARE CF, EuroGentest, EVI-GENORET, LEISHMED, MMR-RELATED CANCER, NEUPROCF, PEROXISOMES, POLYALA, RHORCOD, SAFE, PHGEN and SIOPEN-R-NET.

Portuguese teams contribute to the following European registries: TREAT-NMD, EURO CARE CF and EUROCAT. Portugal contributes to the EUROPLAN project.

Orphan drugs

In Portugal, orphan drugs are the responsibility of INFARMED, the National Authority of Medicines and Health Products. A partnership has been established in 2010 between INFARMED and Orphanet for a periodical update on the orphan drugs approved and commercialised or otherwise available in the country.

Orphan drug committee

No specific activity reported.

Orphan drug incentives

No specific incentives are currently in place.

Orphan drug availability

Data available on orphan drugs shows a variation in the use of orphan drugs in Portugal: according to an INFARMED report²²³, between 2005 and 2006 there was a decrease of 7.6%, and between 2006 and 2008 there was an increase of 37.9% of usage of all orphan drugs available in Europe in Portugal. Data available from the first semester of 2009²²⁴ showed an increase of 21% in the use of orphan drugs in Portugal, when compared with the same period in 2008.

All Portuguese patients have access within from the National Health Service (NHS) to 60 of the 62 orphan drugs approved by the European Medicines Agency; two were rejected, for not showing therapeutic value compared to those already on the market. Of the 62 drugs with a marketing authorisation in Portugal, 3 may be available in retail pharmacy and 59 are exempt only from the hospital. Of these, 18 can be purchased only with Special Use Authorization (SUA), 12 of them because of no interest in marketing to date, and 6 because they are still under evaluation for current use.

It should be noted that access to these drugs or their use without any cost to the patient is not at stake. Of the 12 orphan drugs for which no evaluation was requested, 7 had never been subjected to any request for use, and the 5 remaining were provided by the SUA. The 6 drugs under evaluation were authorised for special use in 138 patients. Of the total of 62 medicines available, 53 were used to date.

The investment of the NHS in orphan drugs in 2010 exceeded 72 million Euros, which represents 7% of the total consumption of medicines in hospitals. It should be noted that there was an increase of 18% in this group of drugs, as compared to 2009. It must be kept in mind that the total increase in hospital spending in 2010 grew only 2.2%, compared to 2009, when including orphan drugs. It must be noted also that 5 orphan drugs account for 65% of expenditures in this group (Imatinib, Bosentano, Galsulfase, Lenalidomida, Sorafenib)²²⁵. 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 (eg, SUA) will have access to therapy.

Other initiatives to improve access to orphan drugs

A Special Use Authorization (SUA) procedure is in place to provide access to certain orphan drugs (see section on "Orphan drug availability").

Orphan drug pricing policy

Orphan drug pricing policy fall under the responsibility of the Ministry of Health.

Orphan drug 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.

Orphan devices

Orphan devices 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 for through public and private funding; many programmes are organised by patient organisations, such as the Portuguese Association for Paramyloidosis.

²²³ *Medicamentos órfãos utilizados*: INFARMED Report (2009) <http://www.acs.min-saude.pt/pns/acesibilidade-ao-medicamento/medicamentos-orfaos-utilizados/>

²²⁴ *Medicamentos órfãos utilizados*: INFARMED Report (2009) <http://www.acs.min-saude.pt/pns/acesibilidade-ao-medicamento/medicamentos-orfaos-utilizados/>

²²⁵ Source: www.infarmed.pt/portal/pls/portal/docs/1/5650244.PDF.

There are some projects to help the integration of patients in daily life, and the 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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

On 29 February 2008, the Romanian Ministry of Health and the country's National Alliance for Rare Diseases (RONARD) signed an accord to form a partnership ("Rare Diseases, a priority for health care in Romania) in order to instate a national plan for rare diseases, following work which started in August 2007 to develop a National Plan, and a National Conference on Rare Diseases in November 2007 on the theme of "Rare diseases: From evaluation of needs to establishing priorities".

A member from the ministry and from the National Alliance for Rare Diseases (RONARD) were appointed to work together to review the national plan which was developed by rare disease stakeholders and presented to the government at the end of 2007, with the aim of creating an estimate of funding and resources required for each element of the plan. An expert team, including geneticists, paediatricians, endocrinologists, pneumologists, cardiologists, haematologists, informatics specialists, public policy experts and other specialists will be gathered to help evaluate the plan and develop a cost analysis for each item. The country's 2008 health budget was then to be readjusted to include funding for various elements of the rare disease plan.

An official decision of the Romanian Government²²⁶ (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 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.

Many informal meetings (June 2009, November 2009, January 2010, April 2010) of the Committee concentrated on the Romanian National Plan for Rare Diseases. As part of the NoRo project initiated and implemented by RONARD, 5 meetings of the members of the National Committee for Rare Diseases were held in 2010 to work on the National Plan. Participants discussed how to improve the quality of life for people with rare diseases in Romania and how to establish a national strategy to ensure adequate measures of prevention, diagnosis, treatment and rehabilitation of patients with rare diseases. The MS Rare Diseases Operative Commission has been established, which is coordinated by National Committee for Rare Diseases, and is involved directly in elaborating and execution of the National Committee for Rare Diseases' decisions.

²²⁶ <http://www.ms.ro/?pag=133>

The major achievement of 2010 was therefore the elaboration of the Romanian National Plan for Rare Diseases²²⁷ which has been transmitted to the Health Ministry, and included in the national strategy for 2011. The next step will be the implementation of the plan.

A National Conference on Rare Diseases, organised by RONARD in collaboration with Eurordis took place in Bucharest, 18-19 June 2010, in the context of the Europlan project. At this conference, a representative of the Ministry of Health gave an overview of the progress made in 2010 regarding the National Plan for Rare Diseases: a diagnostic and treatment programme has been in place since 2008, but it was acknowledged that there is no legislative framework supporting the Plan, and that a resolution is needed in order to implement the National Plan for Rare Diseases in the National Health Strategy (for more information see 'Europlan national conference').

At the end of 2010, Order 1591 /1110/ 30 December 2010 - MH / National Health Security gave the legislative framework for the 8th Health Programme dedicated to rare diseases, in addition to other programmes which indirectly support the patients with rare diseases.

The table below gives an overview of the estimated provisions of a range of regulations related to rare diseases, concerning the estimated number of patients and funding per patient /year in Romanian Lei for the clinical care (including screening, follow-up, etc.), drugs and therapies of these patients²²⁸.

Disease name	Number of patients	The estimated value of the amounts allocated per patient/year (lei)
Haemophilia	1200+60	25000 (1200) + 45000 (60)
Thalassemiias	240	32000
Multiple Sclerosis	2200	42000
SLA	240	15000
Myaesthesia gravis	40	39200
Muscular dystrophy Duchenne and Becker type	150	78400
Spinal muscular atrophy	90	39200
Severe pulmonary hypertension	190	95645
Mucoviscidosis	260 + 50	43660 (260) + 38000 (50)
Osteogenesis imperfecta	25	1684
Fabry disease	4	828437
Pompe disease	1	664036
Tyrosinemia	1	120450
Epidermolysis bullosa	25	6000
Prader-Willi syndrome	61	26615
Phenylketonuria	65	12295
Congenital myxedema	2000	212
Carcinoid syndrome	50	30000
Acromegaly	350	15000
Central Diabetes insipidus	180	1200
Pituitary dwarfism	290	27000
Mucopolysaccharidosis	25	22300

Centres of expertise

There are no official centres of expertise for 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 Chircuta- 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. There is also a network of pulmonary hypertension centres in 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 - Paediatric Cardiology Clinic (Targu Mures), Children's Emergency Hospital "Louis Turcanu" (Timisoara), Heart Centre - Cardiovascular Surgery Clinic (Cluj), Department of Paediatric Cardiology (Bucharest). In addition,

²²⁷ http://www.eucerd.eu/upload/file/Docs/ROPlan_en.pdf

²²⁸ Average rate 4.2 Lei / EUR.

many university hospitals are centres of expertise for several specialities, including in care patients with rare diseases. Many national institutes / regional university hospitals deserves as tertiary care centres for patients with rare diseases. An extension of expertise to have a better 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 been gained around the medical universities and currently many rare diseases are diagnosed and treated. The Operative Commission of Rare Disease recently found around the MH 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 needed for diagnosing and follow-up of the patients with rare diseases, gathered around specialised medical teams involved in this domain.

The Romanian Prader Willi Association is developing a future pilot reference centre in collaboration with the Ministry of Health, using the Norwegian Frambu model. This centre will open in 2011. This initiative is in the context of the NoRo project, whose goals are derived from the National Plan for Rare Diseases, which has been developed in partnership with the Ministry of Health and funded by the Norwegian Programme of Cooperation with Romania.

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.

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 Government²²⁹ 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.

Romania contributes to the EURO CARE CF European registry.

The MS 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.

Neonatal screening policy

Currently neonatal screening is available for two rare diseases, phenylketonuria and congenital hypothyroidism. Despite being part of a National Programme screening for these diseases is not yet available nationwide (due to delay in transportation of samples from local maternity to regional laboratories, deficit of trained staff, low budget, etc.). In 2010 efforts were made via the Health Programme at local level in order to generalise and improve the organisation of neonatal screening for these two disorders as well as to introduce screening for other diseases. The 2010 health policy improved the management of NBS for PKU and CH at local level, reaching 80% coverage for the newborns (around 200,000/ year 2010).

Tests for newborn screening are provided on request by private clinics/laboratories at full cost. Newborn screening for some conditions (e.g. hearing loss) can be carried out in the framework of research programmes.

²²⁹ <http://www.ms.ro/?pag=133>

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 are usually performed in projects.

Diagnostic tests are registered as available in Romania for 29 genes and an estimated 26 diseases in the Orphanet database²³⁰.

Genetic testing can be done 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 labs offer a variety of modern molecular tests for purchase.

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 this.

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.

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. Patient organisations also have the possibility of receiving accreditation as “organisations of public utility”, there is also a procedure in place to authorise the research capacity of a patient organisation. There are certain funding resources for patient organisations’ activities. Patient organisation representatives are able to act as ‘observers’ in different commissions: their representation is recognised but their opinion is not binding and there is usually no financial support for attending meetings.

Rare disease patient representatives from RONARD have contributed to the elaboration of the National Plan for Rare Diseases. Another major achievement is the setup of a call centre (help line) with information available on the services available in Romania.

In addition, many other patients associations have recently been formed: Muscular Dystrophy Association, Congenital Heart Disease Foundation, PKU Life Romania Association, and Romanian Association for Haemophilia, National Association Myasthenia Gravis, Romanian Network of Hereditary Angioedema, Romanian Society for Multiple Sclerosis, Mini Debra Association for Patients, Pulmonary Hypertension Patients Association with Epidermolysis Bullosa, Romanian Association for patients with neuroendocrine tumours.

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.

Since the end of 2010 the scientific advisory board has been 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 information²³¹ for patients and medical experts, encouraging the exchange of information and

²³⁰ Information extracted from the Orphanet database (May 2011).

²³¹ http://www.apwromania.ro/oamenirari/ghid_servicii_en/index.html.

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.

Help line

The Romanian Prader Willi Association/ RONARD also provide and fund an accredited help line: 080 080 1111. This service is also subsidised by the Ministry of Labour.

Other sources of information on rare diseases

The site <http://bolirare.ro/> provides some information on rare and genetic diseases. 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 ("Romanian Journal of Rare Diseases" (www.rjrd.ro)) was also launched in 2010. This publication is the international official journal of the National Committee for Rare Diseases, founded and started as part of the project of the Romanian Prader Willi Association, "The Norwegian-Romanian Partnership (NoRo) for progress in Rare Diseases" funded by the Norwegian Government granted by the Norwegian Cooperation Programme for growth and sustainable development in Romania.

Best practice clinical guidelines

The Romanian Society of Medical Genetics is working to elaborate best practice guidelines for rare diseases in Romania according to European regulations. 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.

Training and education initiatives

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 has been accredited for organising training/ educative courses in the field of rare diseases and these courses will start 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)²³² 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 will start once the Pilot Reference Center for RD "NoRo" is open in 2011²³³.

The MS commission for Rare Diseases foresees 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.

European national conference

A two-day national conference was organised in June in Bucharest (18-19 June 2010) in the framework of the European Project for Rare Diseases National Plans Development (EUROPLAN), co-organised by RONARD (the Romanian RD alliance) and Eurordis. Over 150 participants attended this conference, including physicians (geneticists and GPs), patient organisations, representatives of the Health Ministry and Romanian Physicians' Council, politicians, a Romanian representative at the European Parliament, students and volunteers. The conference treated the following topics: methodology and governance of a national plan for rare diseases; definition, coding and inventorying of RD; research on RD; standards of care for RDs (centres of expertise and European Reference for rare diseases); patient empowerment and specialised services; sustainability; gathering expertise at the EU level. Participants agreed that action should be taken to collaborate with the Ministry of

²³² www.edubolirare.ro

²³³ http://www.apwromania.ro/calendar_curs_2011/

Health in order to implement the Romanian National Plan for Rare Diseases, including a list of priority areas and interventions within the framework of the National Plan. It was suggested that the National Plan for Rare Diseases be included in the National Public Health Strategy. It was also agreed that a National Committee for Rare Diseases should be formed and should include Ministry representatives, medical professionals and patients: the Committee should meet quarterly to help the advancement of plan, in collaboration with the current Norwegian-Romanian 'NoRo' Partnership for Progress in Rare Diseases, funded by Innovation Norway. The final conference report is available on line for public consultation²³⁴.

National rare disease events in 2010

In Romania, the Romanian National Alliance for Rare Diseases RONARD organised a large campaign for Rare Disease Day in 2010. In 2010 events were held in cities across the country including: Bucharest, Timisoara, Cluj-Napoca, Iasi, Craiova, Zalau, Targu Mures, Slobozia, and Oradea. In many places activities to raise awareness on rare diseases and rare disease marches have been organised. Events included a conference for professionals on the theme of rare diseases and an Orphanet presentation at the Paediatric Hospital Sfanta Maria Iasi, a conference for professionals on newborns and rare diseases at the Department of Obstetrics and Gynecology at the Cuza Voda Hospital and additional rare disease events organised by the Orphanet Romania team at the University of Medicine and Pharmacy on 24 February 2010. A student meeting dedicated to rare diseases and Orphanet was organised in April 2010 in Iasi. In addition to these events a national conference entitled "Healthy people and patients - partners for life!" was held on 26 February 2010 in Bucharest. A TV campaign was also launched on 24 February 2010 in conjunction with Rare Diseases Day.

The 3rd National Congress of Medical Genetics was held in Timisoara (22-25 September 2010) and was preceded by a course entitled "Rare Diseases: An Interdisciplinary Approach" which offered a thematic overview of the field of genetics and consisted of lectures, oral presentations, workshops and a poster session. A special session was dedicated to the national plan for rare diseases and rare diseases, and cooperation with groups of patients.

Hosted rare disease events in 2010

The 2nd East European Conference on Prader Willi Syndrome 29-30 October 2010 was hosted in Zalau.

Research activities and E-Rare partnership

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. Funding of research projects was markedly reduced in 2010 and no new calls were launched. There were no rare disease- related calls for projects in 2010. There are currently no fund-raising initiatives for rare disease research in Romania.

E-Rare

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

Participation in European projects

Romanian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, TAG and Care-NMD. A Romanian team contribute/contributed to the EUROPEAN LEUKEMIA NET European research project. Romanian teams contribute to the following European registries: EURO CARE CF and European Registry for CML (EUTOS). Romania contributes to the EUROPLAN project.

Orphan drugs

Orphan drug committee

No specific activity reported.

Orphan drug incentives

No specific activity reported.

²³⁴http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Romanian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

Orphan drug 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 delays in the importation of certain orphan drugs. As a consequence of the creation of the National Plan for Rare Diseases, the Ministry of Public Health enlarged coverage of orphan drugs from July 2008 onwards in their health programme.

The list of orphan drugs commercialised in Romania is available on the website of the Romanian National Medicines' Agency²³⁵ and includes: Aldurazyme, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyf, Gliolan, Glivec, Increlex, Inovelon, Litak, Lysodren, Myozyme, Naglazyme, Nexavar, Onsenal, Orfadin, Pedeia, PhotoBarr, Prialt, Replagal, Revatio, Revlimid, Savene, Siklos, Soliris, Somavert, Sprycel, SUTENT, Tasigna, Thalidomide Pharmion, Thelin, Thromboreductin, Torisel, Tracleer, Trisenox, Ventavis, Volibris, Wilzin, Xagrid, Xyrem, Yondelis, Zavesca.

Orphan drug reimbursement policy

The National Programme for Rare Diseases provides for the reimbursement of 17 orphan drugs in Romania.

Other initiatives to improve access to orphan drugs

In Romania there are several ways of accessing orphan drugs 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.

Orphan drug pricing policy

No specific information reported.

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. Recreational camps have been organised in 2009-2010 by RPWA in cooperation with Werdnig Hoffman Association. 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 Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

National plan/strategy for rare diseases and related actions

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, after in depth discussions in 2010, a working group will be established at the start of 2011 at the Ministry of Health. It will be composed of experts in the field of rare diseases and its main aim will be to work on the "National plan for development of health care for patients

²³⁵ <http://www.anm.ro/ /Lista%20medicamentelor%20orfane%20valide%20in%20Romania.xls>

with rare diseases, “NP RD SR”. The NP RD SR should be ready for the end of 2013. A national conference on rare diseases is planned at this end point.

In terms of practical developments regarding health care in the field of rare diseases in 2010, the Ministry of Health has accepted guidelines for the organisation of health care for people suffering by cystic fibrosis and Wilson disease.

In general, doctors mainly take their own initiatives in this field without advice from guidelines and cases are dealt with individually. Some doctors who take a special interest in a certain rare disease attempt to gather these patients and provide them with appropriate health care in collaboration with foreign institutes on the basis of personal contacts.

In 2009 and 2010, due to the economic crisis, the Ministry of Health froze projects concerning rare diseases and there were no new calls for funding, where there were previously calls to obtain funding for projects concerning rare diseases, including rare disease research.

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), the Centre for metabolic diseases (1), and in several metabolic or specialised outpatient clinics.

Registries

No new registries were established in 2010, but work has started on a registry for alkaptonuria, and work is being carried out on an analysis of health care registries provided in Slovak Republic by National Centre of Health Informations (NCZI) with the aim of extracting data on rare diseases. The registry of congenital anomalies is financed from the budget of Ministry of Health and others receive sponsoring. Slovak Republic contributes to the EUROCARE CF European registry.

Neonatal screening policy

Neonatal screening is available in Slovak Republic for phenylketonuria, cystic fibrosis, congenital adrenal hyperplasia and congenital hypothyroidism. In addition to this, newborns are screened nationwide for hearing impairments. The Screening Centre of Slovak Republic SCN SR is a member of EUNENBS (European Union Network of Experts on Newborn Screening), and results of the activities of the SCN have been presented to this group.

Genetic testing

As a small country, Slovak Republic does not have a large number of laboratories for genetic testing. Genetic testing is organised by the departments of medical genetics (12), specialised genetic outpatient clinics or specialised departments of oncogenetics (2). There are 3 bigger 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 developed at national level. 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 frequently takes place abroad, mainly in the Czech Republic.

Diagnostic tests are registered as available in Slovakia for 51 genes and an estimated 51 diseases in the Orphanet database²³⁶.

National alliances of patient organisations and patient representation

There is no national alliance of patient organisations for rare diseases at the moment in Slovak Republic, although patient organisations for certain rare diseases exist (i.e. Marfan syndrome, muscular dystrophy, haemophilia, cystic fibrosis, Huntington disease, mucopolysaccharidosis, phenylketonuria, Williams syndrome, dystrophic epidermolysis bullosa). There are no public funding schemes for patient organisations in Slovak Republic. There is a small platform for patients to voice their opinions: complaints are usually dealt with on a case by case basis by the “Bureau for control of health care”, and one patient representative will be part of the working group for rare diseases established by the Ministry of Health in 2011. Some patient organisations are members of the NR OZP SR (National Disability Council in Slovak Republic).

²³⁶ Information extracted from the Orphanet database (May 2011).

Sources of information on rare diseases and national help lines

Orphanet activities in the Slovak Republic

Since 2006 there is a dedicated Orphanet team in Slovak Republic, the team was hosted before 2010 by the Institute of Molecular Physiology and Genetics in Bratislava. In 2010, in the context of the Joint Action Orphanet Europe, the Ministry of Health designated the 2nd Department of Paediatrics of the University Children's Hospital Bratislava as the official Orphanet team for Slovak Republic. This team is 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

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.

Best practice clinical guidelines

Best practice guidelines have been developed for cystic fibrosis, Wilson disease and haemophilia.

Training and education initiatives

Currently, there are no training or education initiatives organised systematically in the field of rare diseases/

Europlan national conference

Slovak Republic did not hold a Europlan national conference in 2010.

National rare disease events 2010

With the support of the Faculty of Pharmacy in Bratislava in the context of Rare Disease Day 2010, a number of initiatives were taken to assemble more information about the situation in the field of rare diseases directly from the perspective of patient organisations. Information concerning Rare Disease Day was forwarded to patients organisations together with a short questionnaire. The main aim was to investigate their awareness of rare diseases. The replies are currently being evaluated.

The only regularly organised conference in Slovak Republic related to rare diseases is Izakovic's Memorial Conference, organised every year by the Society of Medical Genetics: the conference did not focus specifically on rare diseases in 2010. The Slovak Cystic Fibrosis Conference is regularly organised every two years since 1999.

Hosted rare disease events 2010

There were no rare disease specific events hosted by Slovak Republic in 2010.

Research activities and E-Rare partnership

Research activities

Currently there are no specific programmes for rare disease research in Slovak Republic.

E-Rare

Slovak Republic is not currently a partner of the E-Rare Project.

Participation in European projects

Teams from the Slovak Republic participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne and Care-NMD. Teams from the Slovak Republic participate, or have participated, in European rare disease research projects including: ANTEPRION and NM4TB. Slovak Republic contributes to the following European registry: EUROCARE CF.

Orphan drugs***Orphan drug committee***

In line with the European law (Parliament and Council Regulation (EC) No 141/2000) Slovak Republic has one regular representative taking part in the monthly meetings of the Committee for Orphan Medicinal Products (COMP) and thus actively takes part in the procedure of designation of medicinal products as orphan medicinal products (OMP) and other incentives oriented in development, research and placing (OMP) on the market.

Orphan drug incentives

No specific activity reported.

Orphan drug availability

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. Slovak Ministry of Health is responsible for pricing and reimbursement of all drugs as well as orphan medicinal products. The reimbursement level is set in a national process named "categorisation". Quarterly a "categorisation list" of all reimbursed drugs is published.

Orphan drug reimbursement policy

In the latest categorisation list (April 2011) detailing reimbursed drugs there are 30 orphan medicinal products (out of 62 registered in the EU and thus in the Slovak Republic, 8 are for paediatric use). The drugs 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".

In the Slovak Republic rare diseases patients are reimbursed for most medications, and the initiatives to improve access to treatment have come from patient organisations, with some governmental support. Orphan medicinal products are mainly fully reimbursed. However the trend is slowly changing, and as more drugs become directly available on the Slovak market, for some drugs patients are asked for their financial participation. Whereas in the previous "categorisation list" only Innovelon required a symbolic co-payment in the current "categorisation" 9 drugs are not fully reimbursed. The highest co-payment is for *Myozyme plc ifo 25x 50 mg* (€287,61), although other forms of Myozyme are without co-payment. However generally the co-payments are minor and orphan medicinal products are mainly covered from public health insurance.

Other initiatives to improve access to orphan drugs

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 were performed in the previous year to stress 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 Pharmacoeconomics²³⁷ and a publications written in English on the topic²³⁸.

Orphan drug pricing policy

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Care services, both government-run and private, are available in Slovak Republic and partial or full reimbursement is available (depending on certain criteria). Therapeutic programmes such as spa stays are available and paid mainly through private health insurance.

²³⁷ <http://www.sukl.sk/sk/o-nas/vzdelavacie-akcie-a-prezentacie/prezentacie-2010/dostupnost-orphan-liekov-v-sr>

²³⁸ Foltánová, T. - Petrová, L. - Mazág, J.: *The need for pricing and reimbursement policy of orphan medicinal products in the Slovak Republic.*

http://www.fpharm.uniba.sk/fileadmin/user_upload/admin/Acta_facultatis/Tomus_LVII/ACTALVIIFoltanova.pdf

1.24. SLOVENIA

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

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. Initial discussions are still currently taking place to explore the possibility of creating a national plan for rare diseases. A new Health Care Act is in preparation which foresees the establishment of reference centres for rare diseases across Slovenia. A working group for the development of a national strategy for rare diseases has been established and a draft national plan was discussed in 2010.

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. A new Health Care Act is in preparation which foresees the establishment of rare disease reference centres. The criteria for the establishment of centres of expertise will be discussed within by the working group for the development of a national strategy for rare diseases, which foresees the establishment of centres of expertise is foreseen in the national plan for rare diseases.

Registries

There is currently no national registry for rare diseases in Slovenia. Slovenia contributes to the EURO CARE CF European registry. 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.

Neonatal screening policy

Neonatal screening is available for phenylketonuria and congenital hypothyroidism. A screening policy is also in place for hearing impairments and developmental dislocation of the hip.

Genetic testing

Genetic testing is offered to patients when there is an indication to perform such tests recognised by a medical specialist. While there are no formally established reference centres in Slovenia, the Institute of Medical Genetics at the University Medical Centre in Ljubljana is the tertiary institution in this area. There are no specific national guidelines regulating genetic testing, those that are deemed necessary are financed by the Health Insurance Institute of Slovenia. In case a specific test not being available in Slovenia, there is a procedure in place, through which patients can obtain approval for reimbursement of genetic testing performed abroad.

Diagnostic tests are registered as available in Slovenia for 47 genes and an estimated 50 diseases in the Orphanet database²³⁹.

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 other national plans, but as there is no national plan for rare diseases in place, this platform does not yet exist for representatives of rare disease patient organisations. 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.

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

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.

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.

European national conference

Slovenia did not hold a European national conference in 2010.

National rare disease events in 2010

In Slovenia, a press conference²⁴⁰ was organised on 26 February 2010 to raise society's awareness of rare diseases, to inform the general public and to improve cooperation between patients and medical profession to improve the quality of life of patients. An article on rare diseases was also added to Wikipedia in Slovenian to mark the event.

Hosted rare disease events in 2010

No specific information reported.

Research activities and E-Rare partnership

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.

E-Rare

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

Participation in European projects

Slovenian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, NEUROPED, TAG, Care-NMD and EN-RBD. Slovenian teams participate, or have participated, in European rare disease research projects including: CONTICANET, EMSA-SG, MYELINET, PNSEURONET and SARS/FLU VACCINE. Slovenia contributes to the following European registry: EUROCARE CF. Slovenia contributes to the EUROPLAN project.

²⁴⁰ <http://vizita.si/clanek/novice/bolniki-in-stroka-za-ustanovitev-sklada-za-zdravljenje-redkih-bolezni.html>

Orphan drugs

Orphan drug committee

In Slovenia, orphan drugs 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 drugs. The Strategic Council for Drugs in 2010 provided additional government budget funds of €1'000'000 to finance two orphan drugs for the treatment of two patients with a rare haemolytic condition and to treat one patient with Hunter syndrome. For the year 2011 a proposal is being prepared for additional funding of two orphan drugs 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 drug 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)²⁴¹.”

Orphan drug availability

No list of orphan drugs registered/ marketed in Slovenia has been provided. Information on the list of reimbursed drugs is available (see below).

Orphan drug 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 drugs 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 2009, the public expenditure for orphan drugs has increased by 28%, which is considerably more than the average increase in expenditure for other drugs. In 2009 (the latest data available) 890 patients were receiving orphan drugs 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 drugs

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.²⁴²”

Orphan drug pricing policy

Pricing of orphan drugs 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 devices

No specific information reported.

²⁴¹ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p19)

²⁴² Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p19)

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 are 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 parallel to this, in 2008 the Spanish Senate launched an official declaration after reaching a general agreement by all political parties where a strong recommendation regarding rare diseases actions was addressed to the Government of Spain. At the beginning of 2008, the Government began to work on a National Strategy on Rare Diseases creating two committees (a Technical Committee made up of 15 scientific societies and 3 patient organisations and an Institutional Committee made up of the representatives appointed by the Health Departments of the Autonomous Communities") which developed the contents of the Strategy. The Spanish National Health System Rare Diseases Strategy was approved by the Interterritorial Council of the Spanish NHS on 3 June 2009²⁴³. It is set within the framework of the Quality Plan of the Spanish National Health System (NHS) which includes, amongst its 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 Spanish NHS Rare Diseases Strategy represents a consensus between the Ministry of Health and Social Policy and Equality, the Ministry of Science and Innovation, 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

²⁴³ <http://www.msc.es/organizacion/sns/planCalidadSNS/docs/enfermedadesRaras.pdf>
http://ec.europa.eu/health/ph_threats/non_com/docs/rare_strategy_spain_en.pdf

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 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. The third part, Monitoring and Evaluation, sets out the process that makes it possible to monitor the proposed actions.

Given the decentralised health administration of 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 and Social Policy and Equality uses the *Funds for the Implementation of Health Strategies* in particular: these funds are used by the Autonomous Communities to implement the new Spanish National Health System Rare Diseases Strategy.

In the area of social services, the year 2009 also saw the creation of the State Reference Centre for Rare Diseases Patients and their Families (Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias, CREER) by the General State Administration, the IMSERSO.

Regional initiatives:

Before the launch of the National Health System Rare Diseases Strategy in 2009, some regional initiatives had already been put in place. The Regional Government of Andalusia (*Junta de Andalucía*) created a genetics plan, the *Plan de Genética de Andalucía 2006-2010*, which, in turn, led to the creation of the *Plan de Atención a Personas Afectadas por ER 2008-2012*, a plan concerning care for people affected by rare diseases.

The Extremadura Autonomous Community approved in December 2010 its Plan Integral de Enfermedades Raras 2010-2014 based on general recommendations from Europe and the Spanish National Strategy. The Health Department of the Autonomous Government of Catalonia (*Generalitat de Catalunya*) recently approved an Order for the creation of an Advisory Commission on minority diseases, 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.). And the Regional Government of Andalusia (*Junta de Andalucía*) continues with the aforementioned *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 regarding care for people affected by rare diseases.

Several Autonomous Communities have started to map their resources in order to elaborate and inventory of expert clinics, 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. Each of the different areas is being developed by groups of experts appointed by the Autonomous Communities, scientific societies and the actual Ministry of Health and Social Policy and Equality. Once the criteria has been agreed a period of CSUR application is opened, and the respective Autonomous Communities can present their proposals through the Designation Committee. Once they have been admitted for processing, the applications are sent to the Spanish NHS Quality Agency for the start of the audit and accreditation process. After the respective accreditation reports have been received, the said Committee studies them together with the other information on each file and submits its proposals for designation, or non-designation, to the Interterritorial Council. The Ministry of Health and Social Policy 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 by the Spanish NHS Quality Agency 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 and Social Policy and Equality have agreed to designate 132 CSUR for 35 pathologies or procedures, including some related to rare diseases. The process continues with other specialisation areas in order to define some more pathologies and procedures, rare diseases included which should be assisted or carried out in CSUR of NHS.

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 Policy and Equality (MSPSI). 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.

Registries

The Spanish Network of Rare Diseases Research on Epidemiology (REPIER) was created in June 2008 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, that since 2008 is part of the Ministry of Science and Innovation, is currently in charge of this registry. This registry is sustained by government financing at the moment. In addition, the Centre for Biomedical Network Research on Rare Diseases (CIBERER) is funding two positions partially devoted to the registry management.

In Spain, there are several population based cancer registries which officially report to the International Agency of Research Cancer of the WHO. Since REPIER was put in place, a specific working group was set up for this particular group of rare diseases as well as for congenital malformations. Both groups are working in collaboration with European and international networks (including EUROCAT) and participate in several European projects.

At regional level, Extremadura has run a registry on rare diseases since 2004. Catalonia has a registry too and Andalusia, the Canary Islands and Castilla-La Mancha are taking steps to develop their own.

Spain also contributes to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, MOLDIAG-PACA, AIR, EURO CARE CF and TREAT-NMD.

Neonatal screening policy

The neonatal screening programme offer differs greatly among Spanish regions²⁴⁴. National neonatal screening is currently in place for phenylketonuria and hypothyroidism. There are 6 Autonomous Communities that have extended the newborn screening programme by Tandem Mass Spectrometry.

A working group with representatives from the Ministry of Health, Social Policy 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 System in 2011²⁴⁵. A previous study was carried out in 2007 by the Public Health Commission of the Interterritorial Council of the Spanish NHS (CISNS) on the situation of newborn screening programmes in Spain, the *Informe sobre la situación de los programas de cribado neonatal en España*²⁴⁶. 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 Spectrometry. It is expected that new European initiatives could provide some guidelines regarding this issue.

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 hereditary metabolic diseases that task was usually carried out by the actual paediatrician or the diagnostic laboratory. These services offer cytogenetic, molecular genetic and biochemical genetic tests (in the case of hereditary metabolic diseases) as well as genetic counselling. The laboratory services are provided by health professionals: medical staff, highly qualified non-medical staff, nursing staff and laboratory technicians; and the genetic counselling services usually 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 areas²⁴⁷.

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 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 (IPTS).

Spanish Law 14/2007 on Biomedical Research defines “genetic testing” as the “procedure to detect the presence or absence of, or change in, one or more segments of genetic material, including indirect tests for the detection of a gene product or other specific metabolite that is primarily indicative of a specific genetic change”. It is estimated that tests are currently available for more than 1000 genetic diseases. Nevertheless, their clinical use has been limited for several reasons. At times there are no external quality assessment services and at others insufficient data is available for their interpretation and validation. But the protocols and

²⁴⁴ 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)

²⁴⁵ “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)

²⁴⁶ “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)

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.

Diagnostic tests are registered as available in Spain for 858 genes in the Orphanet database²⁴⁸.

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 Policy 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.

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 (Centre for Biomedical Network Research on Rare Diseases created, attached and funded by the Institute of Health Carlos III (Instituto de Salud Carlos III – ISCIII). 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 entry point 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.

Official information centre for rare diseases

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

Help line

There is no official help line for rare diseases in Spain.

Other sources of information on rare diseases

The Rare Diseases Research Institute (IIER - ISCIII) developed a public information system named "*Sistema de información sobre enfermedades raras en español – SIERE*" (Information System on Rare Diseases in Spanish) in 2002. There are also plans for updating this system to include epidemiological information by disease.

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, 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. 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,

²⁴⁸ Information extracted from the Orphanet database (May 2011).

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. 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.

Best practice clinical 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. Amyotrophic Lateral Sclerosis, Achondroplasia, Familial Spastic Paraparesis and Aniridia, amongst others.

*GuíaSalud*²⁴⁹ 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 anomalies or skin care in epidermolysis bullosa.

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 59 clinical guides on rare diseases in 2007 and 75 in 2008 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 Diseases²⁵⁰, in collaboration with the Instituto de Salud Carlos III, 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 data²⁵¹.

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 screening²⁵². Originally published as separate articles in the Spanish Health Ministry publication *Revista Española de Salud Pública*²⁵³, 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,

²⁴⁹ <http://www.guiasalud.es/home.asp>

²⁵⁰ <http://dice-aper.semfyc.es/web/index.php>

²⁵¹ The contact person for the protocol is Dr. Miguel García Ribes, coordinator for the working group on Clinical Genetics and Rare Diseases of the Spanish Society of Family and Community Medicine.

²⁵² http://www.isciii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf

²⁵³ http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm

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' during the school year 2010-2011.

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.

Europlan national conference

The Europlan Spanish National Conference on Rare Diseases²⁵⁴ 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 organised by FEDER in collaboration with Eurordis. The conference was attended by a range of stakeholders, the Minister of Health, Social policies and Equality among others who participated in a number of working groups in order to approach the following issues: methodology and governance of a national plan; definition, codification and inventorying of rare disease information and training; research on rare diseases; standards of care for rare diseases, centers of expertise/European Reference Networks; orphan drugs and provision of treatment; patient empowerment and specialised services. All groups 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 online²⁵⁵.

National rare disease events in 2010

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.

FEDER, the Spanish Federation for Rare Diseases, marked Rare Disease Day 2010 with over 200 activities in the context of their annual awareness raising campaign. An event took place at the Spanish Parliament, chaired by President of the Congress, José Bono as well as the First Annual Run for Rare Diseases which was attended by around 2000 people. In addition to these events, the 2nd "Advancing by Research" Meeting, organised by the Biomedical Network Research Centre on Rare Diseases (CIBERER), was held on the 26 February 2010 at the National Center of Cardiovascular Research (CNIC) in Madrid, to celebrate the Rare Disease Day 2010. The main goal was to explain to patient organisations the work carried by researchers in the field during 2009.

The 1st Medical Genetics and Genetic Counselling Conference, organised by Hospital Universitario 12 de Octubre was held on 19-20 April 2010 in Madrid. The scientific programme covered such issues as: congenital defects in rare diseases and their implications, pharmacogenetics and new perspectives in prenatal diagnosis.

Other national events in 2010 included: the III Rare Diseases Congress in Totana (Murcia) organised by Dgenes in collaboration with FEDER on 22-23 October, the IV Annual Meeting of CIBERER (Madrid, 27-29 October 2010) and the Kick Off Meeting of the new Orphanet-Spain Scientific Advisory Board (Madrid, 29 October 2010).

Hosted rare disease events in 2010

Every year since 2000, the Royal College of Pharmacists in Seville has organised the International Congress on Orphan Drugs. This conference did not take place in 2010, but was scheduled for 17-19 February 2011.

Other events announced in OrphaNews Europe included: the Eurordis Round Table of Companies (8 June 2010, Barcelona), the 33rd European Cystic Fibrosis Conference (16-19 June 2010, Valencia), 3rd European

²⁵⁴ http://www.feder.org.es/ver_wysiwyg.php?i=quienes&id=EUROPLAN

²⁵⁵ http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_spain_%20europlan.pdf

Symposium on Rare Anaemias and 1st Spanish Thalassemia meeting for Patients and Professionals (19-20 November 2010, Madrid), 2nd Annual Commercialisation & Market Access Strategies for Orphan & Ultra-Orphan Drugs (15-16 December 2010, Barcelona).

Research activities and E-Rare partnership

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, 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 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 drugs 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 and €5.8 million in 2010 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 National Strategy on Rare Diseases 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 drugs.

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 €5.8 million in 2010 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.

In late 2009, the Sant Joan de Déu hospital and the Hospital Clinic (both of Barcelona) became the first in Europe to establish a biobank specifically for paediatric tissue. The entity seeks to promote the donation of much needed paediatric tissue, such as tendons, bones, skin, cornea, and heart and lung valves. While organ donations for transplant in the paediatric population are more frequent, tissue donations are lacking. Such tissues can be vital to rare disease patients. Working with the Transplant Service Foundation²⁵⁶, the new bank will network with other banks and institutions in Spain and other parts of Europe. According to a news report, the bank has already been authorised to send tissue to the UK's National Health Service.

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 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 has 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).

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 will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Spanish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPI, EPNET, ENERCA (main partner), EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma Network and PAAIR. Spanish teams participate, or have participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BNE, CLINIGENE, CHD-PLATFORM, CONTICANGET, CAV-4-MPS, CureFXS, EMSA-SG EUGINDAT, EuroRETT, ENRAH, EUGINDAT, EUMITOCOMBAT, EUROBONET, EUROGENEST, EUROEAN LEUKEMIA NET, EVI-GENORET, EUROSCA, EPINOSTICS, EUROBFNS, EuroGeBeta, GEN2PHEN, GENESKIN, HSCR, HMA-IRON, LEISHMED, LEISHDRUG, MALARIA AGE EXPOSURE, MCSCS, MOLDIAG-PACA, NANOTRYP, NEUROKCNQPATHIES, MLC-TEAM, PNSEURONET, TRYPOBASE, RISCA, RAPSODI, RD PLATFORM, RevertantEB, SIOPEN-R-NET, SERO-TB, TAMAHUD, TREAT-NMD, and WHIMPath. Spanish teams contribute to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, MOLDIAG-PACA, AIR, EUROCCARE CF and TREAT-NMD. Spain also participates in the EUROPLAN project.

Orphan drugs

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 drugs designated at the European level, this evaluation process is undertaken by all national European agencies under coordination of the EMA, i.e. 'centralised procedure'.

The Spanish High Council for Scientific Research (CSIC), the biggest Spanish organisation performing research, obtained an orphan designation from the European Medicines Agency for raloxifene hydrochloride for the treatment of hereditary haemorrhagic telangiectasia (HHT). It is the first time that a Spanish government agency has obtained an orphan drug designation. Raloxifene hydrochloride activates the endothelial cells of two promoters genes directly involved in HHT. Besides CSIC, research participants include the Institute for Training and Research Marques de Valdecilla, the Biomedical Network Research Centre on Rare Diseases (CIBERER), the Spanish Ministry of Science and Innovation, the Ramón Areces Foundation and the support of the Spanish Association of Patients with HHT.

Orphan drug committee

No specific activity reported.

²⁵⁶ http://www.tsf.cat/eng/quienes_somos/hservicio.php

Orphan drug 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 drugs, 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 drugs,” (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”.

Orphan drug availability

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 (87% of the drugs with European authorisation) and for the rest, the pharmaceutical companies have not yet started commercialisation in Spain.

Orphan drug reimbursement policy

In Spain, when marketing authorisation is granted either by the EMA or AEMPS, the Ministry of Health Social Policies 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 drugs 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, 48 orphan drugs 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 2009, 5 new orphan drugs were included in the national reimbursement list. Moreover, a new law which improves the regulation of compassionate use (particularly for orphan drugs) and foreign medications legally distributed in other countries but not authorised in Spain came into force in 2009.

Other initiatives to improve access to orphan drugs

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.

Orphan drug pricing policy

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

Respite care is provided for rare disease patients considered as living in a situation of dependency. These services can take the form of nursing homes, day care centres, home care, remote assistance, or as a residential stay such as those offered for free at the Burgos' National Reference Centre for Rare Diseases. These services are either public or private and co-payment is often required. Patients suffering from a disability

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 or injury 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 Orphan Drug Regulation definition, a prevalence of no more than 5 in 10, 000.

National plan for rare diseases and related actions

In June 2010, the National Board of Health and Welfare presented a report concerning the organisation of national resources for rare diseases to the Ministry of Health and Social Affairs.

In June 2010, the government decided to establish a national focal point for coordination in the field of rare diseases²⁵⁷, a €300,000 project. The focal point will coordinate rare disease efforts and disseminate knowledge and information within and between health services, NGOs and other stakeholders. The National Board of Health and Welfare is currently finalising the specifications for the national focal point. The decision to establish a national focal point represents an important step towards a better use of the resources available for patients with rare diseases and the patients' relatives.

In November 2010, the Swedish National Conference on Rare Diseases was held in Stockholm, to discuss a future national plan or strategy for rare diseases under the EUROPLAN project (see "National rare disease events").

The National Board of Health and Welfare is currently considering how future work with a national plan 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. National centres of 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.

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 established²⁵⁸ and are supported by the Swedish Association of Local Authorities and Regions (SALAR). All National Quality Registries contain individual-based data concerning diagnosis, treatment interventions and outcomes. These registries are primarily general and do not solely concern rare diseases, although patients with rare diseases may be included, as in, for example, the Swedish Dementia Registry. SALAR encourages managers of registries to apply for funding to become a National Quality Register in order to increase quality of health care on a national level as well as the accessibility of the registry.

The Swedish Association of the Pharmaceutical Industry runs a pilot project that aims to improve the documentation of orphan drugs in clinical use through quality registries. At the moment, this project covers Chronic Myelogenous Leukemia, Idiopathic Thrombocytopenic Purpura and Pulmonary Arterial Hypertension.

²⁵⁷ <http://www.regeringen.se/sb/d/13214/a/148634>

²⁵⁸ <http://www.kvalitetsregister.se/>

Sweden contributes to the EUROCARE CF 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, 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 Umeå²⁵⁹. 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 159 diseases in the Orphanet database.²⁶⁰

National alliances of patient organisations and patient representation

The Swedish National Organisation for Rare Diseases (*Riksförbundet för Sällsynta Diagnoser*) is a national alliance for rare disease patient organisations. The alliance aims to create a holistic view of the common problems associated with rare diagnoses to support small handicap groups, to ease the particular difficulties of patients with rare diagnoses and to promote and protect human rights. *Riksförbundet för 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 för 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 not a specific platform for the representation of or consultation with patient organisations in policy issues for rare diseases in Sweden.

Sources of information on rare diseases and national help lines

Orphanet activities

Since 2006, the Karolinska Institute has hosted an Orphanet team in Sweden. The team collects data on services in Sweden related to rare diseases (for example, specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) for entry into the Orphanet database.

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.

²⁵⁹ <http://sfmg.se/sv/externalankar>

²⁶⁰ Information extracted from the Orphanet database (May 2011).

Official Information Centre for Rare Diseases

Since 1999, the 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 500,000 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.

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. The information is spread through education programmes, at conferences and on their website²⁶¹ and they also provide information by telephone. *Ågrenska* participates in maintaining the Nordic web resource www.rarelink.eu. The *Ågrenska* Academy was established in 2009 and provides streaming live cast lectures and conferences through *Ågrenska*'s website.

Ågrenska has formed The National Competence Centre for Rare Diseases in cooperation with the Swedish National Organisation for Rare Diseases. The centre's main objective is to gather, develop and spread knowledge on rare diseases.

Updated information on orphan drugs has been published by *Läkemedelsindustriföreningen (LIF)*²⁶², the trade association for research-based pharmaceutical industry in Sweden.

The results from the 2009 Swedish EU Presidential Conference on "Assessing Drug Effectiveness" were published in a special booklet²⁶³.

Riksförbundet för Sällsynta Diagnoser has an online database with information on sixty rare diseases.

Best practice clinical 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. These programmes provide education for children, teenagers and adults with rare diseases, their families and for professionals. The aims of the holistic education programmes are to increase and improve empowerment in a lifelong perspective. *Ågrenska* also provides guidance regarding the availability of social services. In 2010, they arranged twenty national family stays such as empowerment programmes, including two educational days for professionals and six national empowerment programmes for adults (adult stays) with a rare disease.

²⁶¹ <http://www.agrenska.se/>

²⁶² <http://www.lif.se/>

²⁶³ www.lakemedelsverket.se

European National Conference

On 11 November 2010, the Swedish National Conference on Rare Diseases was held in Stockholm to discuss a future national plan or strategy for rare diseases under the Europlan project. The conference was organised by the Swedish National Organisation for Rare Diseases in collaboration with Eurordis and attracted more than eighty participants from patient organisations, universities, health care organisations and industry groups as well as health authorities, politicians and social workers. After the morning plenary session, during which time the background to EUROPLAN was presented, four different workshops took place.

The first of these workshops debated whether Sweden should align its rare diseases definition with that of the European Orphan Drug Regulation. This workshop also discussed the World Health Organization's ICD 10 classification, which is currently used in Sweden, and requested that Sweden adopt ICD 11 as soon as possible upon its release.

The second workshop addressed research issues. Suggestions to improve and enhance research included creating a fund dedicated to rare disease research, raising money for the support of rare disease clinical trials (particularly trials with established drugs for new settings and on new disorders), setting up more quality registers and forming national medical centres. New national medical centres would care for patients and also conduct interdisciplinary research, permitting researchers more contact with patients, medical professionals and other health care providers.

The third workshop focused on the centres of expertise and orphan drugs. Regional versus national centres were debated, with the majority supporting the idea of national centres, which would be best developed at university hospitals. Sustainability was stressed. For orphan drugs, the discussions mainly concerned financing. Many in the rare disease community hope that a national fund for orphan drugs will be set up in order to ensure more equal access to orphan drugs throughout Sweden.

Patient empowerment was discussed in the fourth workshop. Many patients asked for help lines and for more informational resources in Swedish, particularly for social issues. The need for greater financing of patient organisations was stressed, as was the importance of including patients in reference groups with the ability to influence decisions. The conference has put rare diseases on the agenda and stimulated the discussion concerning a national plan for rare diseases. The final report of the conference is available online²⁶⁴.

National rare disease events in 2010

To mark Rare Disease Day 2010, the Swedish National Organisation for Rare Diseases led an awareness campaign by placing Rare Disease Day posters in several hospitals and by distributing an informative film produced by the organisation, entitled "Rare, but not unusual".

A meeting organised by *Dagens Medicin*, Sweden's largest paper for medical professionals, took place 25 March in Stockholm. The main topic was the EU's recent recommendations regarding a national strategy and action plan for orphan drugs and rare diseases. The difficulties faced by patients were reviewed. The French strategy was presented and discussed as an example of good practice in the field. Much of the discussion focused on the assessment of marketed drugs which are reimbursed as participants were not content with certain recent decisions on this issue. A report concerning the organisation of national resources for rare diseases presented in 2010 by The National Board of Health and Welfare was discussed. Experts stressed the point that considerations on rare disorders need to extend beyond orphan drug aspects. Several constructive proposals were put forward during the discussions and a high-level politician participating in the meeting declared her commitment to promote the rare diseases issues in the Swedish parliament.

Hosted rare diseases events in 2010

Amongst the rare disease events hosted and announced in OrphaNews Europe were the European Society of Human Genetics Conference and the European Meeting on Psychosocial Aspects of Genetics (12-15 June, Gothenburg) and the Advances in Neuroblastoma Research 2010 Conference (21-24 June, Stockholm).

Hosted Nordic events

A one year project funded by the Nordic Council has investigated possible areas for Nordic networking and cross-country cooperation in the field of rare diseases. On 7 September, *Ågrenska* organised a Nordic conference with the topic to explore the possibility for a more sustainable Nordic network. All Nordic governments were represented and the conclusion was to set up a network and a semi-annual conference revolving among the Nordic countries.

²⁶⁴ [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_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Sweden%20EUROPLAN%20NC%202010.pdf)

A Nordic conference on Dystrophia Myotonika was held on 8-9 September 2010.

Research activities and E-Rare partnership

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.²⁶⁵ 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.

A number of private foundations also support medical research on rare diseases but these grants are not specifically designated to rare diseases.

Research on rare diseases is performed at many universities and university hospitals. This research is supported by grants from the government as well as from non-governmental foundations. Clinical research concerning rare diseases is partly supported by county councils/regions and clinical trials are partly sponsored by orphan drug companies. Some 50 national hospital units and 30 university departments involved in research activities are registered in the Orphanet database.

The Swedish Cancer Society and the Childhood Cancer Foundation are examples of a non-profit organisation which contributes to the funding of cancer research (including rare cancer), information-sharing and supporting activities which aim to improve cancer treatment and care. Research projects are funded following the same policy as that of the SRC.

It is impossible to separate support for rare disease research from support for orphan drug 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. During 2010, a number of scientific papers and investigations have been published. 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 website²⁶⁶ 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.

E-Rare

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

National participation in European projects

Swedish teams participate or have participated in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUOHISTIONET, Paediatric Hodgkin Lymphoma Network and PAAIR.

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, EUROBONET, 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.

Swedish teams contribute to the following European registries: AIR, EUROCAT and EUROCARE CF. Sweden is a partner of the EUROPLAN project.

²⁶⁵ Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp20-21).

²⁶⁶ www.mun-h-center.se

Orphan drugs***Orphan drug committee***

A few Orphan drug expert committees in Sweden have been formed on the initiative of the Swedish Society of Medicine and of local county councils, respectively.

Orphan drug incentives

The Medical Products Agency (MPA)²⁶⁷ is responsible for the regulation and surveillance of the development, manufacturing and marketing of drugs and other medicinal products, including orphan drugs in Sweden.

The MPA can waive the fees for clinical trial applications and provide scientific advice for researchers, applicants and companies lacking support from the pharmaceutical industry. Concerning the provision of free of charge IMP by clinical trial sponsors, Swedish law allows exemptions: should an obligation to perform a trial after marketing have been a condition of the marketing authorisation being granted for an orphan drug. The same could apply for all clinical trials and IMPs, not just orphan drugs on the condition that the clinical trial is performed without the participation of the pharmaceutical industry or that the clinical trial is special importance to public health.

Orphan drug availability

According to the MPA, 50 orphan drugs were sold in Sweden during 2010. These drugs are Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Glivec, Gliolan, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedea, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tassigna, Thalodimide Celgene, Thelin, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Vpriv, Wilzin, Xagrid, Yondelis and Zavesca.

The PDBB has decided to reimburse 30 of these 50 drugs. When a drug is not subsidised, the individual counties decide whether a patient should get access to a treatment. This means that orphan drug availability may vary in different parts of the country.²⁶⁸

Orphan drug reimbursement policy

Reimbursement decisions are made by the Dental and Pharmaceutical Benefits Board (DPBB), 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, orphan drugs 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.

Other initiatives to improve access to orphan drugs

Compassionate use of orphan drugs is being introduced in Sweden and in the future will be the responsibility of the MPA. For orphan drugs 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-orphan drugs.

Orphan drug pricing policy

No specific activity reported.

Orphan devices

No specific information reported.

²⁶⁷ www.mpa.se

²⁶⁸ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 59-62)

Specialised social services

Ågrenska offers families, adults and children the possibility to benefit from educational and holistic activities adapted to their needs as well as individual home visits and assistance. These programmes also provide guidance to orientate patients regarding available social services.

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.²⁶⁹

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 decision²⁷⁰. 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 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

²⁶⁹ <http://www.vgregion.se/upload/HoH/Kansli/R%c3%a5d%20och%20st%c3%b6d/lss-engelska-hso-hoh.pdf>

²⁷⁰ List and criteria are available at www.ncg.nhs.uk

which draws in part on work done by the Specialised Healthcare Alliance²⁷¹ around ethical considerations. Membership of the group is wide-ranging and includes both commissioning and clinical representation, as well as an ethicist²⁷². 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 services²⁷³ (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.

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, there is currently no national plan or strategy for rare diseases in the UK. A national plan will be developed during 2011.

Rare Disease UK (RDUK) is now campaigning for the adoption of a plan for rare diseases. RDUK has been meeting 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 has 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 2010 in Manchester (see section on National rare disease events) to examine proposals for a plan.

The former Chief Medical Officer for England, Sir Liam Donaldson, released his final report²⁷⁴ in 2010. In this report, he brings to the fore the issue of rare diseases in a section entitled *Rare Is Common*. In just seven pages, the report presents a comprehensive overview of the rare disease scenario in England, including statistics, individual portraits, and a synopsis of the major elements of concern: prevention, screening, diagnostics, research, quality of life, management, treatment and cost issues. Six key actions are recommended:

- Strengthen the network of reference centres for rare diseases to enable better coordination of specialist services, including the transition from paediatric to adult services;
- Ensure that adequate numbers of specialists are trained so that future service needs can be met;
- Appoint a National Clinical Director for rare diseases to oversee the development of clear standards and pathways for the treatment and surveillance of rare diseases, with national registers to support service planning and delivery as well as research;
- Strengthen research, including translational research with economic incentives, to develop and market medicines for the ‘orphan diseases’;
- Raise public and professional awareness of this neglected group of diseases;
- Support international collaborative efforts to share information and resources for rare diseases.

²⁷¹ <http://www.shca.info/index.htm>

²⁷² A full list of participants is provided here: <http://www.specialisedservices.nhs.uk/info/agnss>

²⁷³ 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

²⁷⁴ http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_114012.pdf

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 published its latest Scientific Annual Report²⁷⁵ in 2009. 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”. The 2009 report spotlights congenital adrenal hyperplasia, progressive intellectual and neurological deterioration in childhood, and Guillain Barré/Fisher syndrome, amongst other conditions. 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 to 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 report²⁷⁶.

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 as of 1 April 2010, for patients with the following disorders: neuromyelitis optica; Biedl-Bardet syndrome; Barth syndrome; Xeroderma pigmentosum; type 2 neurofibromatosis; cryopyrin associated periodic syndrome (Muckle Wells disease); and glycogen storage type V disease (McArdle disease). National commissioning establishes national centres of expertise for a specific disease and streamlines funding to one centralised source rather than being scattered amongst different local budgets.

Arrangements are in place enabling patients in Scotland, Wales and Northern Ireland to access designated centres although funding is provided by the relevant body in each country. Regional specialist services also exist for genetic diseases but these are funded separately. There is an annual call for applications for national commissioning and designation. Research and epidemiology are not funded under this system.

There has been some criticism from patient groups that the lack of a co-ordinated approach to services for rare conditions engenders late, missed or incorrect diagnoses – sometimes with severe health consequences. A range of wait targets and measures are applied across the NHS: the target of particular importance to patients with rare diseases is the ‘wait’ target (the maximum wait from first contact with a doctor to initiation of definitive treatment). This implies a very strict approach to establishing a definitive diagnosis quickly as this wait is viewed from the patient’s perspective.

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, TREAT-NMD, AIR, EUROCARE-CF, EUHASS, EUROPAC, European Prader-Willi database and EUROWILSON.

Neonatal screening policy²⁷⁷

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

²⁷⁵ <http://www.rcpch.ac.uk/what-we-do/bpsu/publications/annual-reports/annual-reports>

²⁷⁶ <http://www.inopsu.com/publications/INoPSUAnnualReport2009.pdf>

²⁷⁷ <http://www.screening.nhs.uk/bloodspot-compare>

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.

All the molecular and cytogenetic laboratories across the whole of the UK which are part of a Regional Genetics Centre are members of the UK Genetic Testing Network (UKGTN – www.ukgtn.nhs.uk). The focus for the UKGTN is to support equity of access to genetic testing services for patients being treated by the National Health Service for rare inherited conditions. The Network is a collaborative group of genetic testing laboratories, clinical geneticists, genetics commissioners and patient representatives. A small project team and three working groups carry out the work on behalf of the Steering 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 for 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 GEN2PHEN (www.gen2phen.org) and EUCERD (www.eucerd.eu) 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 test 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 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 2010 the UKGTN had evaluated 200 gene dossiers and made recommendation for 159 tests to be available for NHS service. During this time 161 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 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 (MolUs). 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 MolUs 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.

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 476 genes and an estimated 575 diseases in the Orphanet database²⁷⁸.

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.

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 UK²⁷⁹ (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 UK²⁸⁰ (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 document²⁸¹ 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.

In addition, a new RDUK report was published in 2010 highlighting a number of worrying issues experienced by patients and families affected by rare conditions in the UK. The report, *Experiences of Rare Diseases: An Insight from Patients and Families*, presents the views and experiences of 600 patients and families affected by over 100 different rare conditions on a wide range of topics ranging from research to diagnosis, access to care, information, support and treatment. Although some patients and families indicate positive experiences of timely diagnosis and good quality care and support from the National Health Service, such is not the case for the majority of patients and families with rare diseases. Some of the problems highlighted by the report include: significant delays in diagnosis, misdiagnosis (often multiple times), patients *“rattling around the system”* visiting multiple specialists before obtaining an accurate diagnosis, difficulties in accessing information and support, fragmented and poorly coordinated care, patients and families having to attend multiple hospital appointments often at a long distance from home, problems during transition from paediatric to adult services, a lack of effective treatments, inconsistencies in access to medicines, a lack of information and opportunities to be involved in research. The report has been made available online²⁸².

²⁷⁸ Information extracted from the Orphanet database (May 2011).

²⁷⁹ <http://www.geneticalliance.org.uk/>

²⁸⁰ <http://www.raredisease.org.uk/>

²⁸¹ http://www.raredisease.org.uk/raredisease_strategy_consultation.htm

²⁸² www.raredisease.org.uk/documents/RDUK-Family-Report.pdf

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 overview²⁸³ and critique of England's new arrangements for health service commissioning for small patient populations and has developed recommendations to enhance the approach to cost assessment of treatments for these patients. A discussion of the ethical framework that has been introduced to the assessment process for determining cost effectiveness is provided. The Coalition Government 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.

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 UK²⁸⁴ - 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.

On 10 September 2010 the RASopathies Network²⁸⁵ - a patient and clinician partnered initiative - was launched. The RASopathies Network is committed to both supporting families and promoting research, with the aim of improving understanding of all aspects of the conditions and ultimately the development of treatment trials. Given the importance of cooperation in achieving these goals, international collaboration is particularly welcome. This event was the first of its kind to be held in the United Kingdom and signified a culmination of two years' work on behalf of Genetic Alliance UK's Facilitating Networks project, funded by the Department of Health for three years and through which the development of the Rasopathies Network is supported along with five other networks associated with different genetic conditions. The project team has harnessed the hard work, passion and commitment of patient representatives from the Costello Syndrome Support group, Neurofibromatosis Association, BDF Newlife and CFC Syndrome in the UK. While each of the RASopathy conditions is individually classified as rare, collectively it has been estimated that RASopathies account for one in one thousand births in the UK. The support groups have expressed their commitment to engendering a concerted approach to sharing information, raising awareness and facilitating medical research. This patient-clinician initiative is a critical first step in connecting the dots for collaborative international research efforts.

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 a national

²⁸³ <http://www.shca.info/PDF%20files/The%20challenge%20of%20rarity%20-%20FINAL.pdf>

²⁸⁴ <http://www.geneticalliance.org.uk/index.html>

²⁸⁵ <http://ras-pathway-syndromes.com/>

Orphanet entry point for the UK²⁸⁶. This team was officially designated by the Department of Health as the official Orphanet team in the United Kingdom in 2010.

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.

Best practice clinical guidelines

Nowgen (www.nowgen.org.uk) a centre of excellence in public engagement, education and professional training in biomedicine, part of the NIHR Manchester Biomedical Research Centre, in collaboration with Dyscerne (www.dyscerne.org) 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 methodologies²⁸⁷.

A range of other guidelines for rare and very rare diseases are posted on the NCG website (www.ncg.nhs.uk) or published in professional journals.

In July 2009, the *Heart-to-Heart* report, an in-depth needs assessment study of inherited cardiovascular conditions and the services available to treat them in the United Kingdom, produced by the independent non-profit Foundation for Genomics and Population Health (PHG Foundation), was published. Following on from this report, comes the *Commissioning Guide: Services for Patients with Inherited Cardiovascular Conditions*²⁸⁸. Specific to the situation in the UK, the guide nonetheless identifies and discusses many of the general elements necessary to diagnosing and managing patients anywhere with inherited cardiovascular conditions –which include familial hypercholesterolaemia, the arrhythmia syndromes (long-QT syndrome, short-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia); cardiomyopathies (caused mainly by mutations in the proteins making up the contractile system of the myofibrils), including hypertrophic and dilated cardiomyopathies; inherited arteriopathies which cause catastrophic rupture of the blood vessels (Marfan, Ehlers-Danlos, and Loays-Dietz syndromes); and muscular dystrophies (Emery-Dreifuss muscular dystrophy and myotonic dystrophy). The guide divides this family of conditions into five categories, and identifies nine elements essential for providing a comprehensive service for these patients. These include key clinical issues in providing an effective service, treatment, genetic testing,

²⁸⁶ <http://www.orphanet.co.uk>

²⁸⁷ www.dyscerne.org/dysc/Guidelines & <http://www.mangen.co.uk/professionals/clinical-services/useful-documents.aspx>.

²⁸⁸ <http://www.phgfoundation.org/file/5671>

prevention and family care. The components identified are applicable to any country designing comprehensive care for inherited heart conditions – almost all of which are rare.

Training and education initiatives

A training session entitled 'Update in Neuromuscular Disorders' was held for the third year at the National Hospital for Neurology and Neurosurgery (24–27 May 2010, London). 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.

Europlan national conference

The UK National Conference on Rare Diseases, organised by RDUK and Eurordis in the context of the Europlan conference, took place on 16 November 2010 in Manchester. The Europlan conference gathered a range of views from the wide range of stakeholders in attendance on the topics of "governance", "definition, codification and inventorying", "standards of care and centres of expertise", "research" and "patient empowerment". Orphanet was mentioned repeatedly as an invaluable tool and reliable source of information regarding services to support patients and professionals dealing with rare diseases. It was claimed that Orphanet should be supported by the UK government and therefore it should be included in the UK Rare Disease Strategy.

During the workshop views and evidence were gathered about both the situation in the UK currently and how current problems might be addressed through a strategy. A number of examples of good practice were highlighted as well as specific problems in the system currently.

All of the numerous conclusions and ideas were recorded in the final report available online²⁸⁹. The outcomes of the day will also be used for RDUK's report outlining recommendations for a strategy for rare diseases in the UK which will be launched on Rare Disease Day 2011 (28th February 2011).

National rare disease events in 2010

The UK based charity 'Jeans for Genes' holds an annual awareness day to raise funds for genetic disorders²⁹⁰. RDUK organised a number of events to coincide with the 2010 Rare Disease Day, including parliamentary receptions in Scotland (2 March 2010), Wales (24 February 2010) and Northern Ireland (4 March 2010).

An Early Day Motion (EDM 978) for the International Rare Disease Day was tabled by the Parliamentary Member Dr Evan Harris, it read:

"That this House welcomes the third International Rare Disease Day on 28 February 2010; notes that there are over 6,000 rare diseases, affecting approximately 3.5 million people in the UK; supports the focus of this year's Rare Disease Day on the importance of research into rare diseases for the millions of patients without a cure; believes that rare diseases should be seen as a public health priority; and joins Rare Disease UK in calling on the Government to act on its commitment to a strategy for rare diseases as demonstrated by the adoption of the European Council Recommendation on action for rare diseases in June 2009."

RDUK and AMRC (Association of Medical Research Charities) held a joint workshop on 9 December 2010 in Whitehall, London. The workshop tackled the problems that research and development in the field of rare diseases face, including the difficulties that researchers and clinicians face gaining access to funding, as well as the problems that Industry encounters in running clinical trials with very small target populations. The issues that emerged from the workshop included: the importance of finding common ground across rare diseases so that research can be targeted more strategically to "wider conditions", increasing the "rate of success" of grants; the need for assessment exercises to evaluate the impact of charity-funded research; the opportunities and challenges that academic-led clinical trials in gene-therapy for rare conditions offer (these opportunities relate to expertise gathered in public research centres in this particular field of gene-therapy and the Intellectual Property owned by these public institutions); the importance of advocacy networks towards "shaping" policy; and the concept of "venture-philanthropy" as a new form of seeking funding.

Hosted rare disease events in 2010

²⁸⁹ [http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report_uk_europlan.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_uk_europlan.pdf)

²⁹⁰ <http://www.jeansforgenes.com/about>

Amongst the rare disease related events hosted by the UK and announced in *OrphaNews Europe* were: the European Medicines Agency Conference: Sickle Cell - The Next 100 Years (14-16 April 2010, Leicester), 10 years of the Orphan Regulation in Europe (3-4 May 2010, London), European Medicines Agency Workshop on Stem Cell-Based Therapies (10 May 2010, London), the Genetic Interest Group Conference 2010 (8 June 2010, London), 14th International Conference on Behçet Disease (8-10 July 2010, London), the International Data Sharing Conference (20-22 September 2010, Oxford), EFGCP Children's Medicines Working Party and DIA Europe Second Joint Paediatric Conference (28-29 September 2010, London), 2nd European Rett Syndrome Conference (7-10 October 2010, Edinburgh), Encephalitis Professional Seminar (29 November 2010, London).

Research activities and E-Rare partnership

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 stages of research²⁹¹. 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.

In an open access article²⁹² published in PLoS Medicine, researchers from Scotland depict how the "ever-increasing bureaucracy" attached to academic research has imposed a significant obstacle. The situation is critical to research for rare diseases, often shunned by the biopharmaceutical industry due to the inherent lack of profits treatments for low-prevalence diseases afford. Specifically, the authors cite the incorporation of the European Directive 2001/20/EC on clinical trials into UK Good Clinical Practice (GCP) law. Whether or not the elements of this directive are intended for academic clinical trials is not clear, but the number of noncommercial trials has decreased since the UK implemented the new GCP regulations. A survey of eight cancer clinical trial centres reveals that the cost of noncommercial trials has doubled and trials been delayed since the EU regulation came into play. Furthermore, industry has sought to avoid the costs engendered by the increased regulation by moving trials out of Europe. Thus, by the end of 2005, "it was estimated that the number of European trials submitted for grants or ethical review had fallen by 30% to 50% and that the proportion of noncommercial trials was reduced from 40% to 14%". The authors observe that the desired European harmonisation of laws has not materialised and that "the ability...to compete with the better funded US noncommercial trials has been damaged, perhaps irreversibly". In particular, emergency medicine has been impeded, along with noncommercial paediatric trials. Although EU Regulation 1901/2006, which came into force in 2007, was created specifically for the development of medicinal products for children, it insists on full

²⁹¹ <http://www.guysandstthomas.nhs.uk/news/newsarchive/newsarticles/20100512user-involvement-guide.aspx>

²⁹² <http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1000131>

compliance with the Clinical Trial Directive. Citing the phenomenon of “regulatory creep” in which regulations are over-interpreted, the authors instead call for some “regulatory retreat” where “academics try to ensure that the interpretation of any rules and procedures that are not mandated by law are the most favourable for academic research whilst ensuring patient safety”. They invite other areas of the world to learn “from the misguided trial regulations that have been created in Europe”.

E-Rare

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

Participation in European projects

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. 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, EUROBONET, EUROCARE CF, EUROAGENTEST, EUROGLYCANET, EURO IRON1, EUROSCA, EUROTRAPS, EUCILIA, EURO-LAMINOPATHIES, EUNEFRON, EUROPADNET, 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. British teams contribute to the following European registries: EUROCAT, TREAT-NMD, AIR, EUROCARE-CF, EUHASS, EUROPAC, the European Prader-Willi database and EUROWILSON. The United Kingdom contributes to the EUROPLAN project.

Orphan drugs²⁹³

The promotion of the development of orphan drugs in the UK takes place at a European, and not national, level: orphan drugs obtain Marketing Authorisation through the centralised procedure at the EMA. Orphan drugs 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 drug 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.

Orphan drug incentives

No specific activity reported.

Orphan drug availability

No specific information provided concerning orphan drugs registered/marketed in the United Kingdom.

Orphan drug 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 drugs at national level.

²⁹³ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

Other initiatives to improve access to orphan drugs^{294,295}

Orphan drugs, 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 publication *Social Value Judgements: Principles for the Development of NICE Guidance* issued a second edition in July 2008, updating the principles guiding National Institute for Health and Clinical Excellence (NICE²⁹⁶) policy in the UK. The guidance mentions rare conditions in chapter 4, stating that evaluation of products for rare conditions should be the same as for any treatment. However, treatments for “ultra-orphan” disorders (defined by the NHS as conditions or diseases that occur in less than 1 in 50,000 of the population) are to be evaluated by “other mechanisms” that the Department of Health has developed. The document also states that the “rule of rescue” is to be weighed against “the needs of present and future patients of the NHS who are anonymous and who do not necessarily have people to argue their case on their behalf”.

The 2008 audit produced by the Rarer Cancers Forum²⁹⁷, revealed that the system of approving medicines for rare cancers in England is arbitrary, resulting in wide variations in patient access to treatment between different regions of the country. Guidelines for many rare cancers do not exist. This puts the decision in the hands of individual primary care trusts (the agencies responsible for managing healthcare funding locally in England) which often do not have access to information and must rely on an “exceptional case” decision-making process. For rare cancers, the audit found that of 5,000 patients obliged to demonstrate ‘exceptionality’ in the period studied, 1,300 had their requests rejected. Some 3000 patients apply each year for “exceptional funding” for high-priced treatments, often to be used off-licence, and primarily for very advanced cancers. The most requested products include sunitinib (Sutent), erlotinib (Tarceva), cetuximab (Erbix) and bortezomib (Velcade) – all of which have orphan designations in Europe or the USA. There is no nation-wide guidance on how to consistently reach exceptional-funding decisions, and this has resulted in an inequity throughout the land, with some primary care trusts approving all exceptional-funding applications and others systematically refusing identical requests. The report makes several recommendations to alleviate the current situation.

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”.

Orphan drug pricing policy

No specific activity reported.

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.

²⁹⁴ Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

²⁹⁵ 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).

²⁹⁶ <http://www.nice.org.uk/>

²⁹⁷ <http://www.rarercancers.org.uk/index.html>

2. OTHER EUROPEAN COUNTRIES

2.1. CROATIA

Definition of a rare disease

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

National plan/strategy for rare diseases and related actions

There is currently no official strategy or plan in Croatia regarding rare diseases. In 2008, the Croatian Society for Rare Diseases²⁹⁸ 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.

The First National Conference on Rare Diseases (17-19 September 2010)²⁹⁹, organised in the scope of the Europlan conference, allowed stakeholders to meet and discuss priorities for the plan.

Under the auspices of Croatian Minister of Health and Social Welfare, Croatian Society for Rare Diseases of the Croatian Medical Association has organised on 3 December 2010 the First Croatian Symposium on Rare Diseases. Representatives from government, patient organisations' and professionals presented different topics of interest in the development of Croatian National plan for Rare Diseases.

There is currently no earmarked budget for rare diseases in the national health care budget, but special funding is available however for orphan drugs 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 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.

Registries

Currently, there is no national registry for rare diseases in Croatia. 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 registry for birth defects (part of the Eurocat project) covers four regions of Croatia (17% of annual births) and this initiative should soon be extended. Croatia also contributes to the European registry EUROCARE CF. 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".

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

²⁹⁸ <http://www.rijetke-bolesti.org>

²⁹⁹ http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Croatian_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

newborn screening program by tandem mass spectrometry are underway. There are plans to extend metabolic disease screening in 2011.

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 database³⁰⁰.

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 Diseases³⁰¹ 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. 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

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

There is currently no official information centre on rare diseases in Croatia apart from Orphanet.

Help line

There is currently no national rare disease help line in Croatia. Help lines run by patient organisations provide general information for rare diseases diagnostic and management.

Other sources of information

Information on rare diseases is provided by the Croatian Society for Rare Diseases and by institutions hosting the mentioned referral centres. There are also certain public information sources on rare diseases, including help lines and websites run by patient organisations and non-governmental organisations. The site run by the Croatian Society of Patients with Rare Diseases (<http://www.rijetke-bolesti.hr/>) includes information on certain diseases and groups of diseases The Croatian Society for Rare Diseases has developed a website which contains comprehensive information for professionals and patients (www.rijetke-bolesti.org).

Best practice clinical guidelines

No specific activity reported.

³⁰⁰ Information extracted from the Orphanet database in May 2011.

³⁰¹ <http://www.rijetke-bolesti.hr/>

Training and education initiatives

The current university training does not yet provide specific training on rare diseases.

Europlan national conference

The first Croatian National Conference on Rare Disorders was held in Dubrovnik on 17-19 September 2010. Organised by the Croatian Association for Rare Disorders, under the auspices of the President of the Republic of Croatia Ivo Josipovic, and in collaboration with European rare disease patient umbrella organisation Eurordis, the conference sought to bring together patients, their families, association members and multidisciplinary specialists in order to prepare the framework for a national plan for rare diseases (RD) and establish priorities in the field. The conference also provided an opportunity to discuss the problems faced by patients in terms of health and social services. Croatia is the only country outside of the European Union given the opportunity to organise such a meeting in the context of the Europlan project. Some 180 participants were present including patients from 15 patient organisations, health professionals, specialists in rare disorders, and members of the Ministry of Health and Social Affairs, the Croatian Institute for Health Insurance, the Agency for Quality and Accreditation, the Agency for Drugs and Medical Products, the Agency for Education, as well as representatives from the biopharmaceutical industry. Other invitees included Dr. Gabriela Pohla Gubo from the Austrian Debra House and representatives from eight rare disease patient organisations from the Republic of Slovenia, Bosnia and Herzegovina, and Serbia, all of whom are interested in further collaboration with the Croatian Association for Rare Disorders.

The conference programme was conducted through six workshops: Methodology for the development of a national plan for rare diseases); Patient empowerment; Standards in health care for patients; Definition, coding and registration of RD; Research on RD; and Patient rights in social services. Issues such as marginalisation in the health care system, obstacles in social care, critical lack of information and support, access to a multidisciplinary team of experts, delays in diagnosis, the prescription and financing of orphan drugs, dietary requirements, financial problems and other specific issues were amongst the topics featured. There was general agreement amongst participants upon the priority topics to be included in a National Plan and a post-conference questionnaire revealed overall satisfaction with the event. The local media, including television, added visibility to the conference and to the issues rare disease patients and their families face in Croatia.

The final report of the conference is available online³⁰² and details the general proposals and guidelines for actions at national level 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.

National rare disease events in 2010

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.

The Croatian Society of Patients with Rare Diseases and the Coalition of Health Societies organised three days of activities (27 February to 1 March 2010) to mark Rare Disease Day 2010. These events were aimed at raising public awareness of the issues concerning rare diseases. In Zagreb, the capital of Croatia, two days were dedicated to presenting to the public the main issues confronting patient organisations, in the town's market place. On 1 March 2010 a public round table discussion took place including four experts in the field of rare diseases (Professors Ivo Baric, Mirando Mrcic, Ingeborg Barešić and Dr. Lovorka Grgurevic) which was covered by the media. The discussions revolved around current issues, obstacles and achievements in the diagnosis and treatment of rare disease patients in Croatia. The event took place under the auspices of Professor Ivo Josipovic, the President of the Republic of Croatia.

Under the auspices of Croatian Minister of Health and Social Welfare, Croatian Society for Rare Diseases of the Croatian Medical Association has organised on 3 December 2010 the First Croatian Symposium

³⁰²[http://download.eurordis.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/FINAL%20Report_Croatian_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf](http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Croatian_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf)

on Rare Diseases. Representatives from government, patient organisations' and professionals presented different topics of interest in the development of Croatian National plan for Rare Diseases.

Hosted rare disease events in 2010

The following rare disease events were hosted in Croatia this year and reported on by OrphaNews Europe: Second AnEUploidy Workshop (17-19 September 2010, Split), 4th Inborn Errors in Neonatology Course – Orphan Europe Academy (21-23 October 2010, 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.

E-Rare partnership

Croatia is currently not an E-Rare partner and has not yet participated in these calls.

Participation in European projects

Croatian teams participate, or have participated, in the following European Reference Networks for rare diseases: TAG and Care-NMD. Croatian teams participate, or have participated, in European research projects on rare diseases, including: EUROGLYCANET and EUROPEAN LEUKEMIA NET. Croatia contributes to the following European registries: EUROCARE CF and EUROCAT. Croatia contributes to the EUROPLAN project.

Orphan drugs

Orphan drug committee

In Croatia there is no orphan drug 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 drug incentives

No specific activity reported.

Orphan drug availability

The availability of orphan drugs has been improved since the establishment of the Fund for Expensive Drugs at the Croatian Institute for Health Insurance, and a regulation for orphan drugs 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 drugs 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 Products³⁰³. 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 drug 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 drugs are thus now approved

³⁰³ www.halmed.hr

by the Croatian Institute for Health Insurance: all available orphan drugs 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 drugs

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 drug pricing policy

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

There are possibilities for different types of social and respite care services in some parts of the country, although not specifically for rare disease patients, but for those affected with chronic disorders in general: these services are fully reimbursed by national health care. Therapeutic recreational programmes such as summer camps are organised by patient organisations (e.g. children’s camps for those affected by rare forms of solid tumours and lymphomas): this is fully reimbursed by the patient organisation. Social and/or financial support for families and patients with disabilities is regulated by a number of legislative decisions/regulations. Fostering of employment for the integration of handicapped individuals in daily life is partly financed by the government. Recently the National Strategy for Equal Possibilities for Handicapped Individuals 2007-2015 (Class 562.01./07-01/02, No 5030108-07-1, June 2007) was introduced in order to regulate the area of services aimed at the integration of patients with handicaps in daily life.

2.2. NORWAY

Definition of a rare disease

In Norway a medical disorder is considered rare when there are fewer 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.

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 family 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 mechanisms in place in Norway for rare disease patients, a study reveals that more specialist knowledge is needed, along with an “integrated approach” to health care.

In 2008, the Regional Health Authorities 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 in the specialist health services. 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 even more 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 Directorate of Health delivered the report³⁰⁴ on 1 December 2010. The recommendations are supported by the Directorate and the Ministry's approval is expected in 2011.

In addition to this the Regulation on "*approval of hospitals and national services*", which includes centres of expertise for rare disorders, is enforced from the start of 2011: this Regulation would impose the same criteria and demands on centres of expertise for rare disorders as on other national centres of expertise. The document will be translated to English and published where relevant.

Centres of expertise

In Norway there are 16 different state-financed centres of expertise for people with rare and little-known disorders, providing services for more than 16'000 people 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 (RHF) as specialist health care services. The grants to the centres are ear marked through the state budget. The centres report to the Regional Health Authority and to the Directorate for Health.

The Norwegian Directorate for Health has also received the results of a commissioned survey³⁰⁵ carried out by marketing research firm Synovate that sought to explore the knowledge of 11 of the national centres of expertise for rare disorders in Norway. The survey respondents included 139 professionals from local and regional coordinating units, child health clinics, children's units in hospitals and rehabilitation units for children and adults. The knowledge of the different centres varies from 23% to 95% of those surveyed. Variation depends upon the number and type of diagnoses each centre is responsible for as well as the history of the centres. The degree of cooperation with the various centres ranged from 15% to 67%. The most common challenge for those contacting one of the centres of expertise was the need for counselling for a specific and current problem (81%), followed by the need for information about a specific diagnosis (78%), where to be referred for treatment (59%), and how to contact others with the same or similar diagnosis (41%). Some 65% of 106 respondents who had been in contact with one of the centres of expertise stated that the contact concerned a recently-diagnosed patient. 45% stated that their contact concerned a worsening condition, 37% with a transitional stage, 36% with need for information on home care services, and 32% concerned a lack of diagnosis. The respondents asked for information from a variety of professionals: doctors, physiotherapists, nurses, social workers, occupational therapists, educators, genetic counsellors, nutritional physiologists, and social educators. 58% of the respondents familiar with one or more of the Centres of Expertise stated that they or their workplace received counselling via a visit from the centre(s). 51% attended courses or seminars at one of the centres.

Overall, 61% of the respondents claimed that the service from the centre(s) was fairly to very good. 65% experienced the service to be fairly to very relevant. Respondents were also asked about their knowledge of the help-line for rare disorders available at the Norwegian Directorate for Health. The results reveal a lack of knowledge about this free access help-line. Only 37% knew of the help-line, and of these, only 13% had actually called the line.

There was 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, and coordinates and monitors the services for rare disease patients in Norway. The Rehabilitation and Rare Disorders Department at the Directorate maintains a free help-line for rare conditions available to patients, family members and professionals. 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 for certain requests 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 other than the Centre of Expertise. Diagnostics and treatment is principally carried by the ordinary services, while the centres of expertise follow up in the day-to-day aspects of living with a rare disease.

³⁰⁴ http://www.helsedirektoratet.no/vp/multimedia/archive/00316/Revidert_rapport_Sa_316599a.pdf

³⁰⁵ http://www.helsedirektoratet.no/funksjonshemninger/etterlyser_felles_sentral_for_sjeldensentrene_685144

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, patient registry and social security registry). Norway contributes to the EURADRENAL and EUROCARE European registries.

Neonatal screening policy

Neonatal screening for phenylketonuria and congenital hypothyroidism, as well as newborn hearing screening, has been in place for several years. A report from 2008 suggests an expansion of neonatal screening to cover 23 different conditions. This extended newborn screening will be in place from autumn 2011.

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, they are sent to laboratories abroad.

Diagnostic tests are registered as available in Norway for 110 genes and an estimated 119 diseases in the Orphanet database³⁰⁶.

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 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.

Sources of information on rare disorders and national help lines***Orphanet activities in Norway***

Since 2006 the national coordinator for Orphanet in Norway is located at the Norwegian Directorate of Health and is in charge of collecting data on rare disease related services for entry into the Orphanet database.

Official information centres for rare diseases

The centres of expertise develop and revise professionally reviewed information about the different syndromes for which they provide services³⁰⁷. 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 offers 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 relating 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 website (<http://www.helsedirektoratet.no/funksjonshemminger>).

Best practice guidelines

Centres of expertise are involved in preparation of guidelines, directions and guides for rare disorders.

³⁰⁶ Information extracted from the Orphanet database (May 2011).

³⁰⁷ Accessible on these sites amongst others <http://www.sjeldnediagnoser.no/> and <http://www.frambu.no/>

Training and education initiatives

Several Centres of Expertise are involved in different educations and training as medical schools, odontology, nursing schools etc. Some centres administrate web-based courses for specific diseases (e.g. <http://www.sjeldnediagnoser.no/?k=sjeldnediagnoser/home&aid=10960>).

Europlan national conference

Norway did not hold a Europlan national conference in 2010.

National rare disease events in 2010

There are meetings organised at all the resource centres, and annual contact meetings between each centre, their respective regional health authority and the Directorate of Health. Conferences and congresses are arranged on special occasions such as Rare Disease Day. The Norwegian Directorate of Health, HelseDirektoratet, created a web-site to mark Rare Disease Day 2010³⁰⁸. Amongst the national events this year was the Conference on Osteogenesis imperfecta, held in Oslo and organised by the Norwegian Association for Osteogenesis Imperfecta and the TRS Centre for Rare Disorders (22-23 September 2010)³⁰⁹.

Hosted rare disease events in 2010

No other rare disease events were hosted by Norway in 2010.

Research activities and E-Rare partnership

Research activities

National centres of expertise are involved in a number of research projects concerning rare disorders.

E-Rare partnership

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

Participation in European projects

Norwegian teams participate/participated, in the following European Reference Networks for rare diseases: Dyscerne, Paediatric Hodgkin Lymphoma Network, EPNET and Care-NMD. Norwegian teams participate/participated in European rare disease research projects including: CHEARTED, ECFR, EUROCRAN, EURAPS, EURADRENAL, EUROBONET, HUE-MAN, MYELINET, NEUROXSYS, NEUROKCNQPATHIES, SIOPEN-R-NET and VITAL. Norwegian teams participate/participated to the following European registries: EURADRENAL, EUROCAT and EUROCARE-CF.

Orphan drugs

Orphan drug committee

There is no orphan drug committee in Norway.

Orphan drug incentives

As an EFTA/EEA member, the EU orphan drug 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 development of orphan drugs.

Orphan drug availability

By the end of December 2010, 44 orphan medicinal products were marketed in Norway. These drugs are: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Duodopa, Elaprased, Evoltra, Exjade, Fabrazyme, Firazyr, Glivec, Increlex, Inovelon, Kuvan, Mepact, Mozobil, Myozyme, Nexavar, Nplate, Orfadin, Pedeia, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tasigna, Thalodimide Celgene, Torisel, Tracleer, Ventavis, Vidaza, Volibris, 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.

³⁰⁸ <http://www.helsedirektoratet.no/funksjonshemminger/>

³⁰⁹ http://translate.googleusercontent.com/translate_c?hl=fr&sl=no&tl=en&u=http://oi2010.nfoi.no/&rurl=translate.google.fr&twu=1&usg=ALkJrhhd1rxMhQ8SkE0C3PrFFbRqSGOIQ

Orphan drug reimbursement

Norway has an extensive reimbursement system for pricing and reimbursement, and orphan drugs follow these overall principles³¹⁰. However, special consideration can be made for chronic rare diseases (i.e. prevalence < 1/10,000) after individual application for reimbursement.

An open-access article³¹¹ appearing in the *British Medical Journal* depicts the attitudes in Norway towards orphan drug 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 drugs. Furthermore, the authors concede that “*...majority opinion is not necessarily a good measure of what is ethical*”.

Orphan drug pricing

Norway has a structured system for pricing, and orphan drugs follow these overall principles.

Orphan devices

The National Insurance Act (folketrygdloven) gives rights for the use of devices (orphan and common) for daily life activities and work <http://www.lovdato.no/all/hl-19970228-019.html>.

Specialised social services

National rare disease centres of expertise, offer residential 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.

Frambu³¹² offers summer camps for four groups of around 50 children and adolescents each year, offering a chance to meet others in the same 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.

2.3. SWITZERLAND **Definition of a rare disease**

The Therapeutic Products Act (TPA) adopted the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals and this applies for the simplified authorisation of orphan drugs. Stakeholders in Switzerland accept the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10'000 individuals.

³¹⁰ More general information available in the PPRI report *Pharmaceutical Pricing and Reimbursement Information: Pharma Profiles Norway (October 2008)* http://ppri.oebig.at/Downloads/Results/Norway_PPRI_2008.pdf

³¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/20861122>

³¹² <http://www.frambu.no/>

National plan/strategies for rare diseases and related actions

There is currently no national concerted plan or strategy for rare diseases in Switzerland. One of the difficulties in establishing national initiatives and incentives in Switzerland is that, in addition to Federal policy, there are 26 cantons each promoting their own public health policies. Since 1919, the CDS (Swiss Conference of Cantonal Health Directors) provides political coordination, and promotes inter-cantonal cooperation, in the field of health care. Since 2006 the Swiss legislation provides for a simplified authorisation of orphan drugs. In 2007, the Federal Act on Human Genetic Testing (HGTA) became effective, thus regulating the quality of genetic analyses and aiming to avoid discrimination, mainly of patients with rare diseases, and misuse.

On 16 December 2010, Ruth Humbel, member of the Health Commission in the Parliament submitted to the Federal Parliament a postulate for "a national strategy for improving the health situation of people with rare diseases". The decision of the Federal Parliament and the National Council will be announced at the beginning of 2011.

The 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 CDS is Orphanet Switzerland.

Centres of expertise

Several specialised care centres have been established as centres of reference by reputation, usually in University Hospitals.

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, EURO CARE-CF and EUROCAT. Switzerland participates in the following European rare disease research projects: CSI-LTB and NM4TB.

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 the 2-year-pilot project could start in January 2011.

Genetic testing

The medical genetics speciality exists for laboratory directors (FAMH) and for medical doctors (FMH) and several specialised care centres have been established as centres of reference by reputation, usually in University Hospitals. More than 60 public and private laboratories provide genetic testing, although not all tests are reimbursed. Genetic counselling 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 256 genes and an estimated 291 diseases in the Orphanet database³¹³.

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. The official launch of ProRaris, the Swiss Rare Disease Patient Alliance, was announced on 28 February 2010 on Rare Disease Day and ProRaris held its Constitutive Assembly on 26 June 2010, bringing around 100 participants

³¹³ Information extracted from the Orphanet database (May 2011).

representing 42 patient organisations. The participants participated in the adoption of the alliance's statutes and ProRaris' logo was unveiled. The newly elected board of ProRaris spent 2010 working on the new website (www.prorararis.ch), funding for the alliance, the implementation of the secretariat and planning events for the next Rare Disease Day in 2011. The first topics the alliance will address are national level health issues such as health insurance, genetic testing, and orphan medicinal products.

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 Medical Genetics Department of the University Hospital of Geneva. 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

There is no official information centre for rare diseases, however Orphanet is the reference portal for information on rare diseases and orphan drugs in Switzerland.

Help line

There is currently no help line available for rare diseases in Switzerland.

Other sources of information on rare diseases

The 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 CDS.

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

Europlan national conference

Switzerland did not hold a Europlan national conference in 2010.

National rare disease events in 2010

On 28 February a Rare Diseases Day a symposium was organised in Zürich and Basel by the OrphanBiotech Foundation, CheckOrphan and the Gebert RUF Stiftung Foundation. Orphanet and ProRaris were presented in Zürich to representatives of patient organisations and other stakeholders involved in the field of rare diseases.

Telethon Switzerland is a regular, annual fixture and organised a fund raising event at the start of December 2010 for rare diseases.

Hosted rare disease events in 2010

Amongst the rare disease events hosted by Switzerland in 2010 and announced in *OrphaNews Europe* were: the International Workshop on Consanguinity (3-7 May 2010, Geneva), and the World Orphan Drug Congress (29 November – 1 December 2010, Geneva).

Research activities and E-Rare partnership

Research activities

Although there is no specific national budget for rare disease research, the Telethon Suisse raises funds specifically for rare diseases, and research into rare diseases. Moreover, many projects on rare diseases are supported by the Swiss National Science Foundation and a few public foundations (i.e. the Gebert RUF Foundation).

Gebert RUF Stiftung Foundation³¹⁴, a Swiss grant programme specifically for rare diseases, announced its second call for projects in 2010. The independent foundation is committing CHF2 million (€1.3 million) per

³¹⁴ <http://www.grstiftung.ch/en.html>

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 last year, is established as a five-year area of activity. 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.

E-Rare

Switzerland is not currently a member of the E-Rare project.

Participation in European projects

Switzerland has participated and participates in the following European Reference Networks for rare diseases: Dyscerne, ENERCA, EPI/EPNET and PAAIR. Switzerland participates or has participated in European rare disease research projects including: AAVEYE, ANTIMAL, AUTOROME, BIOMALPAR, CLINIGENE, CSI-LTB, CSI-LTB, EMVDA, EURADRENAL, EURO-LAMINOPATHIES, EUGINDAT, EURAPS, EUREGENE, EUROBONET, EUROAGENTEST, EUROGLYCANET, 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. Switzerland contributes to the following European registries: AIR, TREAT-NMD, EURO CARE-CF and EUROCAT.

Orphan drugs

The Swiss Orphan Drug Regulation was introduced in 2006: this regulation stipulates that orphan drug status applies to products treating diseases affecting no more than 1 in 2000 persons. The availability of orphan drugs has been improved since 2006 thanks to the simplified authorisation procedures and the recognition of the orphan drug status for any drug for which this status has been granted in a country with a comparable drugs authority.

Orphan drug committee

No specific activity reported.

Orphan drug incentives

Companies acquiring orphan drug designation for their products are allowed tax exemption for certain administrative taxes but are not however allowed market exclusivity.

Orphan drug availability

No specific information provided on the orphan drugs registered/marketed in Switzerland.

Orphan drug 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 the patient. Based on this case, the Federal Court of Justice decided to fix limits for reimbursements, and although regretting the risk of unfairness, admits that rationing must be introduced. A limit of 100,000 Swiss Francs (€75'000) per year per patient has been set. For each treatment that exceeds the amount specified, the reimbursement will not be guaranteed.

Other initiatives to improve access to orphan drugs

No specific activity reported.

Orphan drug pricing policy

No specific activity reported.

Orphan devices

No specific activity reported.

Specialised social services

No specific activity reported.

2.4. 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 individuals³¹⁵.

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 budget³¹⁶.

In 2010, the Turkish Ministry of Health has 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 actions³¹⁷.

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.

In October 2010 the Ministry of Health organised a workshop on neuromuscular diseases. Medical experts and administrators attended and problems about access to health care, social and psychological problems of patients and issues about especially epidemiological research were on the agenda of this workshop. As an outcome it was decided that 11 centers will be established in different geographic regions in the field of neuromuscular diseases for clinical work-up of patients and that the University Centers which already carry a classification as centers of excellence (Hacettepe and Istanbul universities) will be responsible for training of the medical staff of the new centers and accepting referrals from these new centres. Ongoing

³¹⁵ Communiqué regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

³¹⁶ Notification regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

³¹⁷ Turkey Health Transformation Program

(<http://www.saglik.gov.tr/EN/BelgeGoster.aspx?17A16AE30572D313AAF6AA849816B2EF1DACD7356F6C2568>)
<http://www.orpha.net/actor/EuropaNews/2009/doc/TurkHealthPolicy.pdf>

education and training programs will be organised in clinical diagnosis, pathology, genetic testing and nursing for NMD.

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 TREAT-NMD, CRANIRARE, PODONET 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 2010 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 142 diseases in the Orphanet database³¹⁸.

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.

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.

Best practice clinical 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.

³¹⁸ Information extracted from the Orphanet database (May 2011).

Training and education initiatives

A bylaw has been accepted for fellowship training program paediatric metabolic diseases.

Europlan national conference

Turkey did not hold a Europlan national conference in 2010.

National rare disease events in 2010

Some rare diseases have an annual designated day (e.g. phenylketonuria day, 1 June) to raise awareness of the diseases. The Orphanet Turkey team prepared a press release in order to communicate about rare diseases and Orphanet services to mark the Rare Disease Day 2010 in Turkey.

Hosted rare disease events in 2010

The Society for Study of Inborn Errors of Metabolism's Annual Symposium 2010 was hosted in Istanbul 31 August 2010 – 3 September 2010).

Research activities and E-Rare partnership

Research activities

TUBITAK (The Scientific and Technological Research Council of Turkey) has in the past supported research on rare diseases in Turkey.

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.

Participation in European 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, ELA2-CN, EMINA, EURO-CGD, NEUTRONET and PodoNet. Turkish teams contribute to the following European registries: TREAT-NMD and EUROCARE CF. Turkey contributes to the EUROPLAN project.

Orphan drugs

In Turkey, licencing applications for all human medicinal products are submitted, by accredited licence holders, to the Ministry of Health Directorate General of Pharmaceuticals and Pharmacy, in line with the "Regulation on Licensing 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). 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 drugs and rare diseases in the European Union (EU), studied Regulations 141/2000/EC and 847/2000/EC, and developed a national approach for orphan drug policies in Turkey. The National Draft Guideline for Orphan Medicines was formed as of the first quarter of 2011. The Draft Guideline is currently open for consultation by the pharmaceutical sector.

Orphan drug committee

The Draft Guideline for Orphan Medicines includes the establishment of a "Scientific Commission for Orphan Medicines".

Orphan drug 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 period³¹⁹.

The Draft Guideline for Orphan Medicines will be the first legislative document which to introduce incentives for orphan medicines in Turkey.

Orphan drug availability

At present, the Turkish Ministry of Health (MOH) has not yet developed a national policy with reference to “rare diseases” and “orphan drugs”, 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. Around 20 of the orphan medicinal products authorised in the EU are also licenced for the treatment of patients diagnosed with rare diseases in Turkey.

Orphan drug reimbursement policy

No specific activity reported.

Other initiatives to improve access to orphan drugs

Other EU orphan medicinal products which are not licenced in Turkey can be provided for patient access in Turkey through individual prescription approvals via pre-licencing medicinal product approval procedures.

Orphan drug pricing policy

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 individuals³²⁰.

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.

2.5. 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 governmental lobby for rare diseases was founded in 2009; a law concerning rare diseases has been submitted to the government for consideration.

³¹⁹ Regulation on Licensing of Medicinal Products for Human Use

<http://www.iegm.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=226>

³²⁰ Communiqué regarding the Pricing of Medicinal Products for Human Use

(<http://www.iegm.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

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. Three of these screening tests are provided for free. Many of the tests are reimbursed (specific mutation testing or linkage), but sequencing of genes and array CGH are not reimbursed and patients pay for these tests privately. Genetic testing abroad is possible, but it is not reimbursed and patients pay for these tests privately.

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 recognized by the Israeli Ministry of Health.

Official information centre for rare diseases

No specific information reported.

Help line

No specific information reported.

Other information on rare diseases

There is some information on rare diseases in Israel available on the Ministry of Health Website. Web-based information is available for a limited number of diseases and certain information is maintained using a state budget.

The Community Genetics Department at the Ministry of Health Website, and the Israeli site at the Goldenhelix mutation database

Best practice clinical guidelines

No specific information reported.

Training and education initiatives

No specific information reported.

Europlan national conference

No Europlan conference was held in 2010 in Israel.

National rare disease events in 2010

No specific information reported.

Hosted rare disease events in 2010

No specific information reported.

Research activities and E-Rare partnership

Research activities

There are fund-raising initiatives by specific patient organisations for various rare diseases such as familial dysautonomia, ALS, etc.

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) and will participate in the third call in the context of E-Rare2 in 2011.

Participation in European 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, LEISHMED, MYASTAID, MYORES, NEUROPRION, PWS, STEM-HD, EUROTRAPS, FIGHT-MG, LEISHDRUG, MYELINET, NEURO.GSK3, NEUROSIS, NGIDD, ELA2-CN, EUROGEBETA, RHORCOD.

Orphan drugs

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 drug therapies. Thus these products and patients find themselves competing with general diseases, to their disadvantage.

Orphan drug 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 drug incentives

No specific information reported.

Orphan drug availability

All new drugs (including an Orphan Drug) 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.

Orphan drug 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)

Other initiatives to improve access to orphan drugs

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 drug pricing policy

No specific information reported.

Orphan devices

A draft law on this subject has been proposed.

Specialised social services

No specific information reported.

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³²¹Please note that contributors to the previous report of the EUCERD on “Initiatives and Incentives in the field of rare diseases” have been credited under the heading ‘Contributions in 2010’ and those contributing to the current report have been credited under the heading ‘Contributions in 2011’.

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