

EMINET

Initial investigation to assess the feasibility of a coordinated system to access orphan medicines

Authors:

Claudia Habl
Florian Bachner

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Gesundheit Österreich GmbH / Geschäftsbereich ÖBIG, A 1010 Vienna, Stubenring 6,
phone: +43 1 515 61-0, fax: +43 1 513 84 72, e-mail: firstname.lastname@goeg.at

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Abbreviations

AFSSAPS	Agency for health products (Agence française de sécurité sanitaire des produits de santé, France)
AIFA	Medicines Agency (Italy)
AMGROS	Hospital Purchasing Body (Denmark)
AT	Austria
ATC	Anatomic, therapeutic, chemical
ATU	Autorisations temporaires d'utilisation (Temporary authorisations for use, France)
BAPES	Bulgarian Association for Promotion of Education and Science
BE	Belgium
BG	Bulgaria
CH	Switzerland
CoE	Centres of Expertise
CTS	Italian Technical Scientific Committee
CY	Cyprus
CZ	Czech Republic
DBC	Diagnosis Treatment Combination (Netherlands)
DE	Germany
DG ENTR	Directorate General Enterprise and Trade
DG SANCO	Directorate General Health and Consumers (Direction générale de la santé et des consommateurs)
DK	Denmark
DPS	Drugs Payment Scheme (Ireland)
EC	European Commission
EE	Estonia
EEA	European Economic Area
EL	Greece
EMA	European Medicines Agency
EMINet	European Medicine Information Network
EMTP	Exceptional Medicinal Treatment Policy (Malta)
ERN	European Reference Network
ES	Spain
EUCERD	European Union Committee of Experts for Rare Diseases
EUROPLAN	European Project for Rare Diseases National Plans Development
FI	Finland
FR	France

GMS	General Medical Services Scheme (Ireland)
HU	Hungary
HTMP	High Tech Medicinal Products Scheme (Ireland)
IE	Ireland
INN	International non–proprietary name
IT	Italy
LT	Lithuania
LTI	Long Term Illness scheme (Ireland)
LU	Luxembourg
LV	Latvia
MoH	Ministry of Health
MPS	Mucopolysaccharidosis
MS	Member States
MT	Malta
NCG	National Commissioning Group (UK)
NHS	National Health Service (IT, ES, UK)
NL	Netherlands
NO	Norway
OHE	Office of Health Economics (UK)
PAH	Pulmonary Arterial Hypertension
PCT	Primary Care Trust (UK)
PL	Poland
PPI	Pharmaceutical Price Information (GÖG)
PT	Portugal
RO	Romania
S–Centre	Centre of Expertise (Czech Republic)
SE	Sweden
SEK	Swedish Krona
SHI	Social Health Insurance
SI	Slovenia
SK	Slovakia
SSF	Special Solidarity Fund (Belgium)
UK	United Kingdom

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1 Background and objective

1.1 Introduction

As part of the EMINet Project (European Medicine Information Network), the project leader GÖG/ÖBIG (Gesundheit Österreich GmbH/Geschäftsbereich Österreichisches Bundesinstitut für Gesundheitswesen, Austrian Health Institute) was commissioned by the European Commission (Directorate-General for Enterprise and Industry, DG ENTR) to investigate potential factors contributing to the feasibility of assessing the establishment of a coordinated system for accessing orphan medicinal products (“orphans”) for EU citizens, namely:

- » The purchasing process for orphans in already established national Centres of Expertise (CoE).
- » Derogatory procedures to obtain orphan products outside the regular, i.e. general national reimbursement framework.

The Commission Communication on Rare Diseases: Europe’s challenges¹ and the Council Recommendation of 8 June 2009 on an action in the field of Rare Diseases² both call for coordinated strategies and plans for better treatment of rare diseases in Europe. An important element of this strategy is the Clinical Added Value of Orphan Drugs (CAVOD) based on the Guiding Principles on “Improving Access to Orphan Drugs for Patients in Europe” of the EU Pharmaceutical Forum adopted in December 2008; The principle of exchange of information and non bidding common assessment reports is provided in the Commission Communication when the creation of a Working Party for that purpose is provided in the Council Recommendation; the European Commission has mandated Ernst & Young, based on a EAHC Call for Tender for a “Feasibility Study on the Mechanism to implement the Common Assessment of the Clinical Added Value of Orphan Drugs”; the first conclusions are expected End May 2011. Another key element of this strategy is the establishment of “Centres of Expertise, CoE” (also referred to as centres of reference, centres of excellence or simply specialist clinics), as these are considered to be best suited for treating patients suffering from such diseases. The Member States are encouraged to identify such centres of expertise and to find ways for cross-border collaboration.

About six to eight percent of all EU citizens (27–36 million people) are affected by one of the approximately 6,000 to 8,000 different rare diseases. Although no medical

¹ Council of the European Union 2009

² European Commission 2009

treatment is available for the majority of these diseases, some of them can be treated with orphan medical products. In November 2010 a total of 61 orphan products had received marketing authorisation in the European Union³, compared to 22 authorisations by the end of 2005. The incentives introduced by the European Commission (EC) such as ten (+ two) years market exclusivity, reduced fees for marketing authorisation of an orphan together with free protocol assistance and further national incentives (e.g. in France, Belgium, Italy and the Netherlands) seem to have contributed to this success.

Nonetheless, the 4th EURORDIS Survey on orphan products availability in Europe⁴ demonstrated that access to a selection of these medicines (22 in total) is quite heterogeneous in Europe, with overall lowest availability being encountered in Estonia and Lithuania.

Although various reasons exist for why some orphan medicines are not publicly paid in all Member States, according to EURORDIS⁵, the most important one is the heterogeneity of national reimbursement requirements (e.g. request for additional comparative studies or registries). Moreover limited national health budgets combined with high therapy cost also contribute towards restricted reimbursement. For instance, the annual substance cost for the treatment of a 40 kg patient suffering from Morbus Hunter⁶ with Elaprase (INN: Idursulfase) amounts to around EUR 500,000.⁷

Patient Mobility

As a consequence of growing patient mobility patients with rare diseases are more likely to seek medical care (diagnosis and treatment) in other EU Member States (MS). This affects the consumption pattern of orphans. The Cross-border Health Care Directive which was adopted by the European Council and the European Parliament in January 2011, together with EC Regulations 883/2004 and 897 /2009, strives to facilitate the access to medical and medicinal treatment for patients seeking healthcare in other MS⁸. The Directive is expected to come into effect in 2013.

³ Community Register of orphan medicinal products for human use 2010

⁴ EURORDIS 2007.

In 2nd semester 2010 Eurordis has performed a 5th Survey with a slightly different methodology assessing the situation of the 60 current orphan medicines in 10 MS. Preliminary results confirm that access is still limited.

⁵ www.eurordis.org

⁶ Mucopolysaccharidosis Type II

⁷ GÖG PPI Service 3/2010

⁸ European Parliament 2011; Art. 13 of the Directive explicitly mentions rare diseases and encourages MS to make "... patients, health professionals and payers of healthcare aware of the possibilities offered by Regulation

Currently patients are entitled to receive “scheduled”, medical treatment (e.g. planned surgeries) in another MS 1) if the treatment is covered by their (statutory) health insurance or NHS but is not available in their home country or 2) if the treatment cannot be received in time under given medical circumstances.

In case of a non-emergency hospital treatment abroad, prior approval of the third party payer, for instance health insurance or National Health Service (NHS) of the home country is mandatory. This is to ensure that patients do not have to pay for their treatment including necessary medicines out of their own pocket. To demonstrate that approval was granted, patients are encouraged to present a completed S2 form (previously: E112) to the provider of the service in the MS in which they are planning to access care. The Cross-border Health Care Directive⁹ states that in future prior approval by the national third party payer could also be needed for out-patient health care services requiring a highly specialised and cost-intensive medical infrastructure.

A Eurobarometer Survey published in 2007 showed that on average four percent of all EU citizens had already travelled to another EU/EEA country to obtain medical treatment. Luxembourg (20% of the population) featured the highest rate and Sweden (< 2 %) the lowest rate. The main reason for seeking treatment abroad given by the interviewed persons was “... to receive treatment that is not available in my home country” (91 %). More than half of the interviewed European citizens declared that they were prepared to receive treatment in another country.¹⁰

Due to the large number of affected patients (6–8% of the EU population) the public health impact of rare diseases and orphan drugs is considerable, thus making them an important topic for stakeholders and policy makers. The number of diagnosed patients is growing, resulting in increasing expenditures for medical care. In order to address these issues the establishment of a coordinated access to orphan products was made one of the priority pharmaceutical topics on the agenda of the French, Czech Republic's, Swedish and Belgian EU Presidencies.

At the end of 2010 the EU working group on coordinated access to orphan medicinal products, led by Belgium and DG Enterprise, was launched as part of the newly created platform on access to medicines in Europe. This platform brings together representatives from all Member States, various stakeholders and Commission Services.

(EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation. “

⁹ European Parliament 2011

¹⁰ Flash Eurobarometer 210 (2007)

It was established in the process of promoting corporate responsibility in the field of pharmaceuticals, which follows the European Council Conclusions on “Innovation and Solidarity in Pharmaceuticals”¹¹ of December 2010 based on an Belgian EU Presidency Initiative and builds on the outcomes of the Pharmaceutical Forum.

1.2 Specific objectives and structure of the report

This report focuses on two fields of interest:

1. It provides a mapping and analysis of practices related to the purchasing process of orphans in already established national Centres of Expertise (CoE). As starting point the role and functions of current CoE are introduced in chapter 3.
2. Funding and reimbursement of orphan products in the Member States and in their CoE is presented in chapter 4, giving evidence about 1) who is paying for orphan medicines in CoE, 2) how the centres are purchasing these products and 3) potential implications for national pricing and reimbursement decisions.
3. It examines whether derogatory procedures to obtain orphan medicines outside the “regular” (i.e. general) national reimbursement framework exist (chapter 5) as well as investigating how patients can obtain such treatment outside their home country, especially if the medicine is not available at national level.

Chapter 6 summarises the findings and outlines implications for Member States and stakeholders, presenting these in form of lessons learned.

The main target groups of the report are national public bodies, institutional representatives and stakeholders dealing with pharmaceutical issues in Europe, in particular the participants in the afore mentioned Platform on access to medicines in Europe.

¹¹ www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/.../118278.pdf

2 Definitions, sources and methods

The information presented in the report relies on both primary and secondary data. Secondary data were obtained through a literature research of official regulatory documents and scientific articles.

Primary data collection took place via two surveys conducted by GÖG in summer 2010:

- » The assessment of the current situation regarding the function and role of Centres of Expertise as well as the analysis of the procurement process of orphans in such centres is based on a number of semi-structured interviews with stakeholders and representatives of Centres of Expertise of 16 countries.
- » CoE were selected following the indication of two selected orphan products which were chosen according to predefined criteria (cf. section 2.2).
- » Interviews were conducted via telephone or in written form (e-mail) between July and early October 2010 using a predefined field manual. In several cases (e.g. Czech Republic, Ireland, Hungary, Malta and Austria) the information provided by the interview partner was complemented by further information collected from national pricing and reimbursement authorities.
- » The survey on derogatory procedures applied for orphan medicinal products was conducted online via the EMINet website¹². Survey results were complemented by a literature analysis.

2.1 Definitions

Rare disease

No global definition for rare diseases exists, apart from the fact that they are always characterized by specific (low) disease prevalence. The EU defines a disease as rare if no more than 5 per 10,000 (1 in 2,000) persons are affected within the population. A rare disease is often life-threatening or chronically debilitating and partly inherited.

This definition is accepted by a growing number of Member States, yet there are countries which have established their own definitions: Examples are the UK that uses a prevalence of 1 in 50,000 inhabitants whereas Sweden and Denmark determined a proportion of one affected person in 10,000.¹³

¹² www.emi-net.eu/surveys/index.php?sid=84161

¹³ European Commission 2010b

Orphan medicines (“Orphans”)

A medicine is designated as an orphan product if the following conditions are met:¹⁴

- » It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 per 10,000 persons in the community when the application for marketing authorisation is made, or
- » it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and
- » there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, the medicinal product will be of significant benefit to those affected by the said condition.

Availability and Accessibility

The PHIS glossary¹⁵ defines accessibility as “the patient's ability to obtain medical care” and as “a measure of the proportion of a population that reaches appropriate health services. The ease of access is determined by such components as the availability of medical services and their affordability to the patient, the location of health care facilities, transportation, and hours of operation and cost of care. Barriers to access can be financial (insufficient monetary resources), geographic (distance to providers), organisational (lack of available providers) and sociological (e.g. discrimination, language barriers). Efforts to improve access often focus on providing/improving health coverage.”

In this report accessibility is determined by three factors: 1) the medicine in question has obtained marketing authorisation (in case of orphan medicines via the centralised procedure), 2) it has been launched (i.e. marketed) by the company (receiving marketing authorisation) in a given country and 3) it is available to the patient without administrative hurdles.

Availability of an orphan product for a patient can take two different forms which can both be subject to specific conditions and/or reimbursement regulations (e.g. involving co-payments or particular prescribing requirements):

¹⁴ Article 3 of EC Regulation N°141 /2002

¹⁵ PHIS Glossary 2010b

- » Availability via the regular (general) out-patient reimbursement system, for instance inclusion of the orphan in the country's positive list(s), national formulary or in the general reimbursement schedule;
- » Availability via the in-patient system, e.g. in a Centre of Expertise or inclusion of the medicine in a hospital formulary / positive list.

Derogatory reimbursement procedures

A derogatory reimbursement procedure is any reimbursement regulation deviating from the general reimbursement procedure or in-patient treatment schedule applicable for medicines in a given country. Typical derogatory procedures involve obtaining prior approval from the (public) payer before a service is granted, conditional prescribing, the enrolment of patients in a specific therapeutic programme, or the mandatory involvement of a defined specialist for the disease. In some countries the consultation of a Centre of Expertise (for a definition see Chapter 3) is required. Derogation from the general reimbursement system may also be related to the marketing authorisation or the launch status (commercialised or not) of the product. In some cases derogation can also result in a change of the payer of the medicine in question.

Compassionate use, off-label use and named patient access

Although a medicine may only be distributed in a Member State if it has obtained marketing authorisation, a few exemptions from this rule exist. In specific, legally defined cases patients may obtain un-authorised medicines – even outside clinical trials – via 1) compassionate use, 2) off-label use, and 3) on a named patient basis:

- » **Compassionate use** refers to the application of a medicine that has not yet obtained marketing authorisation, but has applied for it or is undergoing a clinical study in a late stage for a group of patients with life-threatening, long-lasting or seriously disabling diseases. Further conditions for compassionate use are that patients are expected to benefit significantly and that there is no other product authorised for the specific indication. The responsibility for the establishment of compassionate use programmes rests with the individual Member States and is subject to national rules and legislation. Before patients may receive treatment with unauthorised medicines (including orphans) their doctor has to contact the relevant national authority and has to follow the corresponding procedures. The national authorities have to record patients treated as well as any side effects in national registries.¹⁶
- » **Off-Label use** describes the prescription of an already authorised medicine for an unapproved indication, dose, and mode of administration or age group.

¹⁶ REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:EN:PDF>

- » Another way of obtaining medicines without a marketing authorisation is on a **named patient basis**. In contrast to compassionate use programmes the doctor (or CoE) requests supply of the medicine directly from the manufacturer for a specific (“named”) patient under his or her direct responsibility. Manufacturers need to keep track of patients treated.

Summarising, the above mentioned regulations are intended to allow access to medicines, including orphans, before or without obtaining marketing authorisation. But as marketing authorisation is often a pre-requisite for the inclusion of a medicine in the positive list or national formulary, the above mentioned cases usually involve a derogatory reimbursement procedure. Such derogation could, for instance, be exercised by applying specific prescribing rules or may result in a different payer being responsible for the medicine in question (cf. chapter 5 for details).

It is important to be aware that – even if an orphan has obtained marketing authorisation – this does not necessarily mean that it is launched (i.e. marketed or commercialised) immediately by the marketing authorisation holder in all MS. Medicines made available to patients in such a pre-launch situation are colloquially sometimes also called “compassionate use”.

2.2 Products for further analysis

To demonstrate the current state-of-art provision of orphan products in CoE in Member States two products, namely Tracleer (INN: bosentan) and Myozyme (INN: alglucosidase alfa) were selected for further analysis. Product selection took place in a two-step process that involved members of the EMINet Evaluation Committee, as well as EURORDIS¹⁷ (an alliance of patient organisations) and ORPHANET¹⁸ experts (see “Selection of CoE”) based on the following criteria:

- » One “old” and one “new” orphan medicinal product
- » One orphan should be primarily used in an in-patient setting, the other in an out-patient setting
- » One of the products should have an indication with different pharmaceutical treatment options (e.g. pulmonary arterial hypertension, PAH).

Tracleer “... is a medicine that contains the active substance bosentan. It is available as orange and white ‘film-coated’ tablet (round: 62.5 mg; oval: 125 mg) and as pale yellow clover-shaped dispersible tablet (32 mg). Tracleer is used to treat patients with

¹⁷ www.eurordis.org

¹⁸ www.orpha.net/consor/cgi-bin/home.php?lng=EN

class III pulmonary arterial hypertension (PAH) to improve exercise capacity (the ability to carry out physical activity) symptoms. PAH is abnormally high blood pressure in the arteries of the lungs. The 'class' reflects the seriousness of the disease: 'class III' involves marked limitation of physical activity."¹⁹ PAH has a prevalence of 1.5 cases per 100,000 inhabitants in the EU.

Tracleer obtained marketing authorisation via the centralised procedure in May 2002 and is thus one of the first European orphan medicinal products. In contrast to most orphan medicinal products Tracleer can be used in home treatment. Nonetheless, most countries have implemented safeguard mechanisms and have interlinked the dispensing or even the reimbursement of Tracleer to prior consultations of specialists in CoE (see chapter 4).

Myozyme "... is a powder to be made up into a solution for infusion (drip into a vein). It contains the active substance alglucosidase alfa. Myozyme is used to treat patients who have a type II Glycogen storage disease called Pompe's disease (Morbus Pompe), a rare inherited disorder. Patients with Pompe's disease do not have enough of an enzyme called alpha-glucosidase. If the enzyme is not present, glycogen builds up in certain tissues, particularly the muscles, including the heart and diaphragm (the main breathing muscle under the lungs). The progressive build-up of glycogen causes a wide range of symptoms, including an enlarged heart, breathing difficulties and muscle weakness."²⁰ The disease can appear at birth (infantile form) with an incidence of about 1/57,000 but also later in life (adult form) with an incidence of 1 out of 138,000 persons.²¹

Myozyme was granted marketing authorisation in March 2006 and is used primarily in hospitals in the vast majority of Member States. Like most other enzyme replacement therapies Myozyme is quite expensive, causing average treatment cost of 300,000 to 500,000 Euro per year and patient. Currently no alternative medicine exists.

2.3 Survey in Centres of Expertise

The selection of Centres of Expertise (cf. chapter 3 for a definition) to be surveyed was undertaken via ORPHANET, an internet database which offers information on rare diseases and orphan medicines to the public. Orphanet provides a list of expert clinics including contact information listed by indication or disease. The database contains

¹⁹ EMA 2010a

²⁰ EMA 2010b

²¹ www.orpha.net → Glycogen storage disease type 2

Europe based clinics which need to meet predefined criteria such as the presence of a multidisciplinary team and extensive clinical research expertise. In order to be listed on Orphanet clinicians can apply by providing adequate proof of their expertise. All applications are reviewed by each country's scientific advisory board.²²

An Orphanet search for expert clinics in all Member States, Switzerland and Norway resulted in a list of **216 expert clinics dealing with Pompe's disease and 79 clinics specialising in the treatment of PAH.**

The analysis of the results showed that several clinics did not offer personal contact details or that the information provided required updating. These centres were excluded from further investigation, especially when other centres were available in the country. Several of the listed centres were located in the same hospital and were headed by the same persons (e.g. as paediatric department and as centre for metabolic disorders). In this case only one of the indicated CoE was contacted in order to avoid cross posting. When Orphanet listed more than one expert for a CoE, all indicated persons were contacted if contact details were available. Table 2.1 gives an overview of the expert clinics found via Orphanet for Pompe's Disease and PAH.

Based on the contact details found at Orphanet a total of 180 experts specialising in the treatment of pulmonary arterial hypertension (80 experts) and Pompe's disease (100 experts) were contacted.

It is important to mention that patient numbers for the selected diseases PAH and Morbus Pompe differ significantly from country to country. While most EU-15 MS reported slightly increasing numbers of patients every year, this is not the case in most new MS, in which sometimes no patient has been diagnosed so far: For instance only one patient has been diagnosed with Morbus Pompe and treated with Myozyme in Romania whereas nobody had been diagnosed in Estonia, Bulgaria and Latvia until September 2010.

No expert clinic could be identified for Pompe's Disease in nine countries and for PAH in 14 countries while France has listed 42 and 71 clinics respectively. This reflects that in the majority of Member States the process of identifying, establishing and designating Centres of Expertise has not started yet or is still in a very early stage.

Of the 100 contacted experts specialising in the treatment of Pompe's disease (Glycogen storage disease type II) 23 experts replied. These were from a total of 15 countries.

²² www.orpha.net (there is at least one Orphanet expert in each EU country)

Table 2.1:
Number of CoE/expert clinics found via Orphanet, 2010

Country	Number of Expert Clinics	
	Pompe's Disease	PAH
Austria	6	1
Belgium	20	1
Bulgaria	4	0
Cyprus	2	1
Czech Republic	0	1
Denmark	1	0
Estonia	3	0
Finland	0	0
France	71	42
Germany	46	16
Greece	8	1
Hungary	2	1
Ireland	2	0
Italy	8	1
Latvia	0	0
Lithuania	0	0
Luxembourg	0	0
Malta	0	0
Netherlands	3	1
Norway	2	0
Poland	1	1
Portugal	7	1
Slovakia	0	0
Slovenia	0	0
Romania	2	0
Spain	11	6
Sweden	0	0
Switzerland	3	1
United Kingdom	14	4
Total	216	79

PAH = Pulmonary arterial hypertension

Source: Orphanet, prepared by EMINet team 2010

In the case of PAH, 17 CoE from eight countries responded. Addressed experts were asked to recommend other centres in their home countries or in other EU/EFTA countries which could not be found in Orphanet. As a result one additional CoE for Pompe's disease in Latvia and one CoE in Ireland could be identified successfully.

Table 2.2:

Responding countries: Access to and provision of orphan products in European Centres of Expertise

Indication	Responding countries
Pompe's Disease (Glycogen storage disease type II) – Myozyme (INN: alglucosidase alfa)	AT, BE, BG*, FR, DE, DK, EE*, ES, IT, LV*, IE**, PL, PT, RO, UK
Pulmonary Arterial Hypertension, PAH – Tracleer (INN: bosentan)	AT, DE, ES, FR UK, IT, IE**, HU

* Currently no patient in treatment

** Centre was not found via Orphanet but by expert recommendation

Source: EMINet Survey 2010

2.4 Survey on derogatory reimbursement procedures

In order to assess the access to orphan medicines in Member States and to identify potential derogatory procedures related to the reimbursement²³ of orphans an online survey was conducted via the EMINet website.

Following a pilot with the Members of the EMINet Evaluation Committee²⁴ the online survey (cf. Annex 1) was circulated to all EU/ EFTA countries in May 2010.

Table 2.3:

Responding countries: Survey about derogatory reimbursement procedures

Responding countries
AT, BE, CZ, DK, EE, ES, FI, FR, HU, IE, IT, LT, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK, IS, NO → 22 responders

Source: EMINet Survey 2010

Responses were received by 22 countries (response rate: 73.4%) by the end of October 2010. In a few cases national pricing and reimbursement authorities (e.g. from Belgium, Czech Republic, Italy or Hungary) were contacted for clarification.

²³ Definition: Reimbursement is the percentage of the reimbursement price (for a service or a medicine) which a third party payer pays. So 100% reimbursement means that the third party payer covers 100% of the reimbursement price / amount of a medicine or service except a possible prescription fee (PHIS 2010b)

²⁴ Czech Republic, France and Sweden

3 The role of Centres of Expertise in EU countries

“When diseases are rare, expertise is scarce as well.”²⁵

When defining the concept of Centres of Expertise (CoE) for rare diseases the heterogeneity of national health care systems becomes especially evident. As mentioned in section 2.1 neither a common definition of “rare disease” nor a commonly accepted definition of “Centre of Expertise” exists for the 27 Member States of the European Union. Currently established Centres of Expertise are usually characterised by:

- » being located in (university) hospitals (mostly as hospital departments) or being affiliated to one and by
- » being specialised in the diagnosis and treatment of a rare disease or a group of rare diseases.

In some countries Centres of Expertise are also referred to as Centres of Reference, Centres of Excellence or simply expert clinics. For the purpose of this report and for further discussion the expression Centre of Expertise (CoE) will be used for all of the aforementioned types of centres.

It is currently up to the Member States to identify appropriate CoE in their countries. Ideally CoE develop expert knowledge that can be transferred to other centres within the same country or even internationally. Centres should furthermore guarantee patients access to appropriate healthcare.

Although the concept of CoE has not been officially defined by the majority of Member States, efforts have been made by initiatives such as the High Level Group on Health Services and Medical Care (established 2004 by DG SANCO) and the EU Rare Disease Task Force to clearly define criteria and characteristics of CoE. According to these initiatives the following criteria define a CoE:²⁶

- » Appropriate capacities to diagnose, to do follow-up and manage patients with evidence of good outcomes when applicable
- » Capacity to provide expert advice on diagnosis and management
- » Capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control

²⁵ European Commission 2008

²⁶ RDTF 2008

- » Attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for common diseases; or national coverage
- » Demonstration of a multi-disciplinary approach
- » High level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities
- » Strong contribution to research
- » Close links and collaboration with other expert centres at national and international level and capacity to network

The set-up and size of CoE differs considerably in the EU, depending on the national policy framework as well as the focus and function of the respective CoE (e.g. is the centre only in charge of genetic counselling or is full medical service available).

A number of countries have introduced national policies for rare diseases (BG, DK, FR, IT, ES, SE). Some MS, for instance France, have already appointed official CoE in this context.²⁷ The European Union recommends the development of national plans, which also include the identification of CoE for rare diseases, to all Member States by 2013.²⁸ When mapping the European landscape regarding the existence and role of CoE, three different models were identified (cf. Figure 3.1):

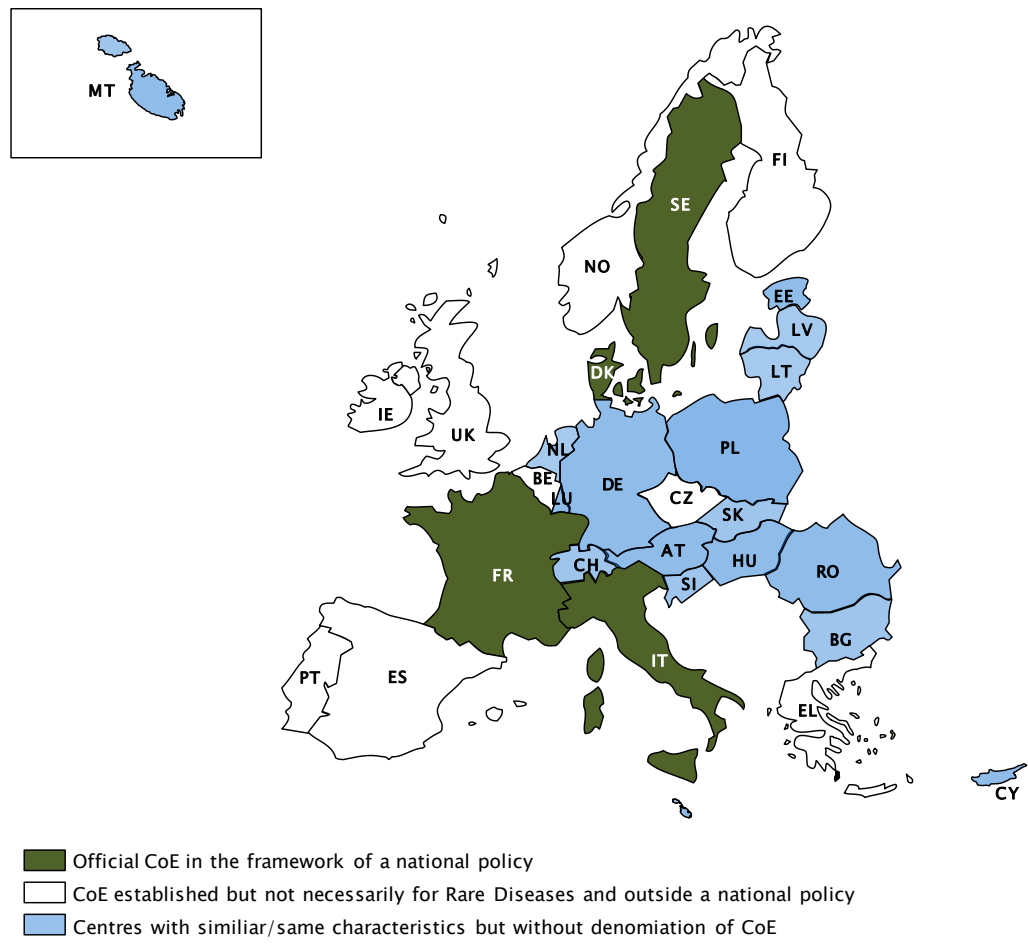
- » In most countries with a national rare disease plan, CoE are officially denominated Centres of Reference. Patients should primarily consult such centres in order to receive appropriate diagnosis and treatment (DK, FR, IT, SE). In selected countries, for instance in France, reimbursement of orphan products is only granted if patients consult an official Centre of Reference or obtain their initial prescription in such a centre.
- » A few European countries have established CoE but have done so outside of the national policies or plans. These CoE are not (always) specifically for rare diseases. Examples for such countries are BE, CZ²⁹, FI, EL, ES, IE and the UK.
- » Other MS have specialised clinics without the denomination as CoE but acting as such (AT, BG, CY, EE, DE, HU, LT, LV, LU, NL, PL, RO, SK, SI, and MT).

²⁷ European Commission 2010b

²⁸ Council of the European Union 2009

²⁹ Acc. to the Czech Rare Disease Strategy no network of specialised centres for rare diseases and no single concept or definition of the services offered by such centres exists. It is planned to develop such concepts as part of the national plan for rare diseases. Several specialised centres of reference (so-called S-centres) however exist such as the National Reference Centre for the Research and Treatment of Gaucher's disease, the National Centre for the Diagnosis and Treatment of Cystic Fibrosis, the Centre for the Diagnosis and Treatment of Fabry's Disease, the Centre for Pulmonary Hypertension, etc.

Figure 3.1:
Forms of Centres of Expertise in the EU 2010



EMINet Survey 2010; RDTF 2008

The EMINet Survey 2010 shows that for Pompe's disease all 23 responding CoE from 15 Member States regularly monitor their patients and provide long term treatment. In addition, all responding centres reported that they diagnose this type of disease as well as other Lysosomal storage diseases initially. Nine CoE reported that they engaged in research activities.

In the case of the enzyme replacement therapy for Pompe's disease the treatment with Myozyme does often not take place directly at the CoE but rather in other hospitals or sometimes also in out-patient clinics close to the patient's place of residence. This means that the place where patients consult experts is not necessarily the place where they receive their medical treatment with Myozyme. A few countries reported that

Myozyme is also given as home treatment following an initial in-patient stay lasting several months.

Looking at Pulmonary Arterial Hypertension (PAH) therapy the situation is similar. 14 of the 17 responding CoE from eight Member States reported that they provided all of the above mentioned services: research for the indication, initial diagnosis of patients, long-term treatment of patients and regular monitoring ('follow-up') of patients.

Following a recommendation of the Council of the European Union adopted on 8 June 2009³⁰, all Member States are encouraged to identify CoE and to strengthen the knowledge sharing between such centres. Bearing this in mind, together with the fact of growing patient numbers, the role of CoE could become even more prominent in the future. Almost all countries replying to the EMINet survey 2010 confirmed growing patient numbers.

European Reference Networks

Besides the creation and identification of CoE at national level, the European Commission is encouraging the development of European Reference Networks of Centres of Expertise (ERN). Such networks are defined as physical or virtual networks of knowledge and expertise of national CoE that exist in more than one European country.³¹ Especially in the field of rare diseases the sharing of expertise among the MS is crucial as knowledge and expertise are as scarce as the disease. Because of the great number of different rare diseases and given existing budgetary limitations CoE may not be established for each rare disease in every country. This increases the likelihood of patients being diagnosed or even treated in countries other than their home country.

Examples of existing ERN are the European Centres of Reference Network for Cystic Fibrosis (www.ecorn-cf.eu) or the European Network of Centres of Expertise for Dysmorphology (www.dyscerne.org). Both of these receive funding from the European Commission. Such ERNs bring together experts from nearly every country of the EU and guarantee the exchange of up-to-date expertise. If sustainable funding is guaranteed, a ERN could be the starting point for future joint activities including joint purchasing of the necessary medicines or of in-vitro-diagnostics (IVD) needed for initial diagnosis and testing. In the future, ERN could fulfil an important interface role regarding the coordinated provision of care for selected patients with rare diseases, especially in the light of cross-border health care. For Pulmonary Arterial Hypertension and Morbus Pompe no ERN could be identified.

³⁰ Council of the European Union 2009

³¹ EURORDIS 2010

4 Provision and funding of orphan medicines in Europe

4.1 Overview of access to orphans

Responsibility for pricing and reimbursement of medicines rests with the MS, as for all pricing and reimbursement decisions. Considerable variations regarding the access, availability and prices of orphan products have been documented, e.g. by the EMINet Orphan report 2009 or by the EURORDIS survey in 2007. It is likely that also the places of delivery, national purchasing policies and mechanisms of public funding for such medicines vary significantly.

The situation has remained more or less unchanged since 2007: In the EMINet survey 2010 only 5 of 22 responding countries declared that publicly funded access to orphan products was always granted if needed and 11 countries stated that access was granted in most cases, but could be subject to specific conditions such as the prior approval of the initial prescription by a CoE or other administrative regulations.

Five responding countries, including all Baltic countries, stated that access was limited due to budgetary constraints. Slovenia noted that for some of the most expensive treatments public coverage was not guaranteed.

Nonetheless, patients in none of the 22 surveyed countries have to pay orphans completely out-of-pocket.

Table 4.1:
Most common access to prescribed and publicly funded orphans in the EU, 2010

	Via the general out-patient reimbursement system	Via a specific out-patient reimbursement system, e.g. particular rules are applicable		mainly provided in hospitals	Provision limited due to budgetary constraints
AT	No	Yes	Prior approval of health insurance necessary	Yes	No
BE	No	Yes	Prior approval of health insurance necessary	Yes	No
CZ	Yes	Yes	Orphans are mainly dispensed in S-Centres	Yes	No
DK	No	No		Yes	No
EE	Yes	No		Yes	Yes
ES	Yes	No		Yes	No
FI	Yes	No	For out-patients access is granted if the therapeutic value	Yes	No

	Via the general out-patient reimbursement system	Via a specific out-patient reimbursement system, e.g. particular rules are applicable		mainly provided in hospitals	Provision limited due to budgetary constraints
			is demonstrated and the price is reasonable		
FR	Yes	No	Access could be linked to the approval of the initial prescription by a CoE	Yes	No
HU	Yes	Yes	Patient named access to some orphan products	No	No
IE	No	Yes		Yes	No
IT	Yes	No		No	No
LT	No	No		No	Yes
LV	No	No		Yes	Yes
MT	Yes	Yes		No	No
NO	No	Yes		No	No
PL	No	No		Yes	Yes
PT	Yes	No		Yes	No
RO	Yes	No		Yes	Yes
SE	Yes	No	For out-patients access is granted if the therapeutic value is demonstrated and the price is reasonable	No	No
SI	Yes	Yes		Yes	No*
SK	Yes	Yes	Access can be linked to the prescription by a specialist	Yes	No
UK	Yes	No		No	No

CoE = Centre of Expertise, S-Centre= Policlinic, i.e. an out-patient department of a hospital in the Czech Republic; can take the form of a CoE

Note: Respondents were requested to ignore orphan products currently undergoing clinical studies.

* Slovenia commented that for some of the most expensive treatments coverage is not guaranteed.

Source: EMINet Survey 2010

Most responding countries apply special regulations regarding the provision of orphan medicines. This is due to the majority of orphans being prescribed and dispensed in hospitals (and their affiliated CoE) as Table 4.1 shows.

Despite the key role hospitals and CoE play in the provision of orphans 15 countries declared that at least some of the marketed orphans were part of the national positive list or their National Health Service national formulary. This is also the case in countries that did not respond to the survey like Germany or Bulgaria. The inclusion of any medicine in a positive list does not necessarily mean that it is fully paid by the public payer or sickness fund, co-payments in various form are possible. In some countries also hospital-only medicines are included in the national formulary or positive list. Consequently, the reimbursement overview in Table 4.2 needs to be interpreted with caution.

Table 4.2:

Availability of EMA authorised orphan medicines in selected Member States in November 2010

	Authorised*	Available through the regular reimbursement system**
AT	61	13 (21.3%)
BE	61	40 (65.6%)
BG	60	18 (30.0%)*
CZ	61	30 (49.2%)
DK	61	47 (77.0%)
EL	61	42 (68.8%)
FI	61	25 (41.0%)
HU	61	13 (21.3%)
IE	61	22 (36.1%)
LV	61	0 (0.0%)
NL	61	43 (70.5%)
NO	61	47 (77.0%)
SE	61	29 (47.5%)
UK	61	43 (70.5%)

* Orphans authorised prior to EC Regulation N°141/2002 as for instance BeneFIX (coagulation factor IX) in Belgium are not counted.

** Availability is defined as orphan products being included in the national general reimbursement list(s) or schedules, i.e. positive lists and national formularies. In some countries, for example in Bulgaria or Denmark this includes the distribution of medicines in hospitals.

*** Data as of June 2010

Note: In addition to the availability of orphans in the national regular reimbursement system, in several countries (e.g., AT, FI) a number of orphans are only available in hospitals and thus included in the list above.

Source: National pricing and reimbursement formularies/databases, PPI 2010

It is important to understand that even if a product is not included in a national formulary or positive list it may still be reimbursed by the national public payer by the way of derogation. For orphan medicines this is often the most common case (cf. section 5.1 for a description of the situation in the responding countries).

Major reasons for orphans to be not included in the national formulary or positive list are:

- » The orphan has not yet received marketing authorisation and is made available to patients via compassionate use or similar programmes (e.g. temporary authorisations for use (ATU) in France).
- » The orphan, despite being authorised, is not (yet) available in a country because
 - 1) no patients have been diagnosed (e.g. with Pompe's disease in Estonia & Latvia)
 - 2) commercialisation requires administrative clearance by the country's authorities (setting of a price, decision on reimbursement rate, actual inclusion in the pharmacy sales list, for example).

- » The marketing authorisation holder did not apply for reimbursement (e.g. Glivec, (INN: imatinib mesilate) in Austria, or Myozyme (INN: alglucosidase alfa) in Finland).
- » Reimbursement was denied by the authorities (e.g. Kuvan) in Sweden).
- » Reimbursement procedure is pending.

Further reasons for deviations in the number of “generally” reimbursed orphans as shown in Table 4.2 are varying cross-country definitions of positive lists and national formularies. For instance, the Bulgarian positive list³² has a section on hospital medicines where 18 orphans were listed in summer 2010 and the orphans included in the Danish national formulary are also mainly for hospital use. The Austrian, Hungarian, Dutch and Swedish positive list does, on the contrary, not contain medicines predominantly used in hospital, being accessible to patients there. In the Netherlands, for instance, least eight further orphans are available in hospitals.³³

It is also relevant to know that the inclusion of a medicine in the general reimbursement system does not automatically mean that it is 100% funded by the respective public payer or that its use is not linked to certain conditions: For instance, the reimbursement of some orphans included in the regular reimbursement system of Sweden or Finland³⁴ is linked to conditions such as second-line therapy. Also, the fact that no orphan is included in the Latvian formulary does not mean that none are accessible to patients.

³² BAPES 2010

³³ OHE 2009

³⁴

4.2 Access to Tracleer and Myozyme in the EU

The following examples of the access to Tracleer and Myozyme show the scope of regulations existing in the Member States.³⁵

Prescribing: Due to the rareness of the diseases and the limited number of specialists in some countries only specialists working in a CoE or a comparable institution are allowed to prescribe orphan products. Their approval may be required in case another specialist prescribes an orphan.

For Tracleer and Myozyme this is the case in **France, Italy, Germany, Slovakia** and the **UK**. Patients with Pompe's disease in the UK have to consult one of eight national CoE in order to obtain NHS-funding for Myozyme. In Germany any prescription of Tracleer requires approval by a second specialist of a social insurance (second opinion) in order to be reimbursed by social health insurance.

Reimbursement: A large number of Member States covers the total cost of Tracleer and Myozyme (AT, BE, BG, CZ, DE, DK, ES, FR, HU, IT, NL, PL, PT, SK and the UK). In some countries reimbursement is subject to certain conditions or is only granted partially.

In **Finland** full reimbursement is granted for Tracleer in the case of hospital treatment, and, because of the Finnish consumption-based out-patient reimbursement system, also for PAH patients who self-administer Tracleer.³⁶ In **Norway** Tracleer and Myozyme are, like all other orphan medicines, reimbursed by 62%. For children younger than 12 years, for low income pensioners and for patients who have reached the co-payment ceiling of 65 Euro per quarter full reimbursement applies. **Sweden** has set up a system of so called high-cost thresholds whereby a medicine is tax-subsidised, meaning the state covers a defined share of the costs. Also patients will never need to pay more than SEK 1,800 / EUR 193 for prescription medicines during any twelve-month period (expenditure cap).³⁷

³⁵ Based on MS interviews and results of the EMINet Survey on orphan products conducted in 2010.

³⁶For all PAH-medicines the reimbursement rate is 72%. When total annual cost for reimbursed prescription medicines exceeds € 675/patient, patients are granted 100 % reimbursement for rest of that year and only need to co-pay € 1.50/pack/purchase. In the case of Tracleer the annual limit is exceeded the first time a patient goes to pharmacy to buy the product.

³⁷ Swedish High-Cost-Thresholds: Product priced up to 900 SEK: the patient pays 100% of costs up to 900 SEK; Products priced between 900–1,700 SEK: the patient pays 50% of the cost, 900–1,300 SEK; Products priced between 1,700–3,300 SEK: the patient pays: 25% of the cost, 1,300–1,700 SEK; Products priced between 3,300–4,300 SEK: the patient pays 10% of the cost, 1,700–1,800 SEK; Products > SEK 4,300: the patient pays 0% of the cost, 0 SEK (TLV 2010)

In **Italy** and **Portugal** patients need to be enlisted in a register in order to receive reimbursement for Myozyme. In Portugal all patients with a confirmed diagnosis of Morbus Pompe who are treated with Myozyme have to be approved and monitored by the National Coordination Centre (a Commission nominated by Minister's decree).

Distribution: In case a prescription is issued by a CoE this does not necessarily mean that the product is also dispensed by the CoE. In a number of Member States most orphans are also available via community pharmacies (in practice this could mean that the orphan is not reimbursement if not bought in the determined preferred place of use).

In **Belgium**, **Denmark** and the **UK** Tracleer and Myozyme as well as all other orphan medicines are only distributed through hospitals and their pharmacies (except for Glivec and Thalidomide in **BE**). **France** applies a special policy for selected products such as Tracleer which allows hospital pharmacies to dispense orphan products also to out-patients. In **Finland** home treatment with Tracleer is provided in case the patient is able and willing to self-administer the medicine. In this case Tracleer can be purchased directly from a public pharmacy. Finnish Pompe' patients are treated in hospitals only.

4.3 Funding orphan medicines in CoE

The predominant sources of funding for orphan medicines in the EU Member States are Social Health Insurance Schemes or the National Health Service (NHS), both at federal or regional level.

Respondents to the EMINet 2010 survey explained that the funding of orphan medicines dispensed in CoE was usually similar to the general funding mechanism applicable to other medicines in the hospital (CoE are usually located in a hospital or affiliated to one). Table 4.3 provides an overview of the main payers of orphan medicines in hospitals as well as listing special regulations in place in case the orphan is not included in the "regular" hospital funding system.

Table 4.3:

Funding of medicines and orphans in hospitals in the EU

Country	Main payer for orphan medicines in hospitals	Special funding/reimbursement for orphan medicines in hospitals
AT	SHI and provinces via provincial health funds	(Regional) sickness funds pay a lump sum for hospital services to the provincial health fund. This fund allocates the budget to the public hospitals in its region. The budget includes expenditure for all pharmaceuticals used in these hospitals. Two provinces signed agreements with the regional sickness funds stating that the cost of selected high cost medicines (incl. orphans) will be covered by the regional sickness fund even if they are dispensed in the in-patient sector.
BE	SHI	Hospitals are funded via a combined fixed budget and fee-for-service system. Hospitals operate pharmaceutical formularies. If an orphan is not included in the Belgian formulary (e.g. because it is not yet authorised or launched) patients can request treatment via compassionate use programmes or apply for reimbursement through the so called Special Solidarity Fund.
BG	SHI, state and public hospitals	The hospital use section of the positive list (paid by the SHI) includes 18 orphans. Further 11 may be accessed outside the general reimbursement scheme based on ministerial order N ^o . 34 (paid by the state and hospital budget, respectively). Moreover selected orphan medicines are donated (for free) by their manufacturers (cost-free products).
CY	State (for public hospitals), out-of pocket (for private sector unless coverage via private insurance)	If an orphan product is not included in the Cypriot positive list, patients can request reimbursement via (compassionate use) programmes financed via the state budget and will receive treatment in hospitals.
CZ	SHI	In addition to orphan products generally being reimbursed compassionate use programmes for non authorised medicines are in place. Such programmes are often coordinated by a CoE (S-Centre) and funded by the hospital.
DE	SHI	After authorisation all launched orphans are fully reimbursed in the German health system. Medicines used in hospitals are usually covered by the DRG system. For very expensive products outside the DRG system the sickness funds have to pay the hospitals separately ("Zusatzentgelte").
DK	Regions (via state subsidy)	Orphans not included in the pharmaceutical list of a hospital can be covered by the regions in case of 'compassionate' or named patient use (for patients with life threatening diseases) upon prior approval of the Danish Medicines Agency. Various forms of personal subsidies are possible
EE	SHI	There is no specific funding outside the general hospital funding system.
EL	SHI	Selected orphans are explicitly funded by the Hellenic Drug Organisation (EOF) and the Institute of Pharmacological Research and Development (IFET): Fabrazyme, Replagal, Glivec, Tracleer, Trisenox, Aldurazyme, Ventavis, Myozyme, and Siklos.
ES	Depending on owner; SHI or NHS (via regions)	All orphan products commercialised in Spain are fully covered by the NHS. This is also true for compassionate use of non authorised products.
FI	Municipalities	Orphans provided in public hospitals are funded by the municipalities (based on taxes) and user fees (~ EUR 50/day including medicines)

Country	Main payer for orphan medicines in hospitals	Special funding/reimbursement for orphan medicines in hospitals
FR	SHI	Medicines dispensed in hospitals are included in the hospital budget derived by an activity based funding system. Certain high cost medicines (Liste en sys) including most orphans are excluded from this system and are reimbursed separately (70–100%) by the health insurance funds.
HU	SHI	The payer of orphans in out-patient care, the National Health Insurance Fund also funds orphans used in hospitals (part of the hospital budget).
IE	NHS (for public hospitals)	A small number of funding arrangements exists as consequence of which individual hospitals are designated as national centres and are thereby protected from the financial implications of the cost incurred by orphans.
IT	NHS (via regions) and AIFA fund	All EMA authorised orphan products are reimbursed by the regions. Off-label and compassionate use programmes are in place. A special fund for orphans, operated by the AIFA, exists.
LT	SHI	The compulsory health insurance fund pays for orphan medicines on basis of case by case decisions using an earmarked budget.
LV	SHI and state (for medicines on basic list)	One percent of the public medicines' budget is intended for medicines used for the treatment of rare diseases (not necessarily orphan products). Certain high-cost orphans are either covered by the hospital budget or, in case the hospital budget is too small, by the state budget. In case of unavailability of an orphan in one hospital patients may be transferred to another hospital.
MT	State	There is no specific funding outside the general hospital funding system.
NL	SHI	Hospitals receive their budget from a so called Diagnosis Treatment Combination system (in Dutch: DBC). The assigned budget depends on the patient's diagnosis. However, orphans on a predefined list with expensive medicines are not subject to the DBC system, but have to be reimbursed separately by social health insurance at 100%.
PL	SHI	Pharmacotherapy for hospitalised patients is financed by the National Health Fund including orphan products. Medicines are part of the hospital budgets. For highly specialised services (e.g. grafting or special pharmaceutical treatment) a separate state budget is provided or special therapeutic programs are available.
PT	NHS / state	Medicines used in hospitals or in CoE are funded from a different budget than out-patient medicines. Expenditure for Myozyme is paid directly to the hospital by the ACSS (a Portuguese payment entity of the Ministry of Health). Myozyme and other Lysosomal storage disorders treatments have been allocated a dedicated budget. A National Coordination Centre nominated by decree approves and monitors such treatments & patients.
RO	SHI	There is no specific funding outside the general hospital funding system.
SE	Regions/County Council	Orphans used in hospitals are subject to case by case decision on hospital or county level as such medicines are not included in the regular (out-patient) reimbursement system. As a consequence availability of orphans may vary between counties. Due to the unequal distribution of patients a solidarity funding between the county councils was put in place for 2 rare diseases (Gaucher's Disease and haemophilias).

Country	Main payer for orphan medicines in hospitals	Special funding/reimbursement for orphan medicines in hospitals
SI	SHI	Medicines in in-patient care are paid from the hospital budget but certain high cost orphans are excluded from this regulation. The Health Insurance Institute pays for these orphans based on individual assessment (case-by-case decision). The Slovenian Health Committee (Annual agreement between representatives of hospitals, health insurance and the Ministry of Health) decides about the payment for certain indications, for a determined number of patients, by a predefined scheme and in a specific hospital e.g. university hospital, specialised hospital.
SK	SHI	Hospitals receive a fixed amount of funding for every in-patient from health insurance companies, depending on the type of hospital and the patient's indication. These payments include the cost of medicines. As every health insurance company has a separate contract with the hospitals, remuneration amounts vary. Moreover health insurance companies purchase some medicines (e.g. growth factors or beta interferons) directly if these are used in selected centres in hospitals.
UK	NHS (via primary care trusts)	The NHS pays for launched orphan medicines through primary care trusts (PCT) subject to available funding. Certain orphans are funded directly by the NHS Specialised Services (NCG) at national level; however these orphans can also be reimbursed by the PCT. As a result access to orphan products can vary depending on the place of residence of the patient. It is possible to import unlicensed orphans on an individual named patient basis.

AIFA = Italian Medicines Agency, NHS = National Health Service, orphan medicinal products = orphan medicinal product, PCT = Primary Care Trust, SHI = Social Health Insurance

Source: EMINet 2010, EMINet 2009, PHIS 2010, KCE 2009, EUCERD 2010

Only few countries distinguish between orphans and other medicinal products when funding or reimbursing pharmaceuticals in CoE. In Poland, for instance, therapeutic programmes are an important source of funding for expensive medicines including orphans. In Italy orphans and also CoE are funded by the regional NHS. In addition, in 2005 the Medicines Agency AIFA set up a fund of about EUR 45 million a year, of which half is devoted to the reimbursement of orphan and 'life saving' medicines.

Only few countries have special laws or mechanisms which apply to all marketed orphan medicines. In contrary, considerable differences in the overall funding and reimbursement strategy for orphans as well as the actual number of orphans reimbursed exist. For example, in 2008 only seven orphans were reimbursed in Bulgaria whereas e.g., in France, in Spain, in England or in Germany the majority of all launched orphans were available for any patient in need. However, access is often linked to special conditions and in many cases subject to conditional reimbursement (case-by-case decisions).³⁸

³⁸ OHE 2009

4.4 Procurement of orphan medicines in CoE

4.4.1 Overview of purchasing situation in Europe

In times of limited health care budgets and growing financial pressure pricing and procurement of medicines are a major topic on the agenda of national and European stakeholders. Especially the procurement process of medicines is of essential importance in this context since it may have a direct influence on the price of the medicines and can affect national budgets.

The majority of European countries (24 of 27 MS) apply price control policies such as external price referencing resulting in statutory prices. National price regulations often include the remuneration of intermediaries, for instance wholesalers or pharmacies. In most European countries this also applies to medicines used in the in-patient sector. A few countries, however, do not regulate prices of medicines in hospitals (e.g. DK, DE, PL, UK).

In hospitals, and thus in affiliated CoE, any price regulation only concerns the maximum hospital price (list price). This list is in practice often reduced in the purchasing process especially for medicines where competition is established (e.g. patent expired). As a result real prices paid by hospitals are often lower than the maximum price. As actual prices paid by hospitals are neither publicly available nor shared with other hospitals, details on prices differences in hospitals are rare. Analytical reports such as the PHIS Hospital Pharma Report 2010 show significant differences in this context.³⁹ It emphasizes the importance of having the right procurement strategy as this can result in the achievement of considerable price reductions, ranging from zero to sometimes even 100 percent (see chapter 4.2.2).

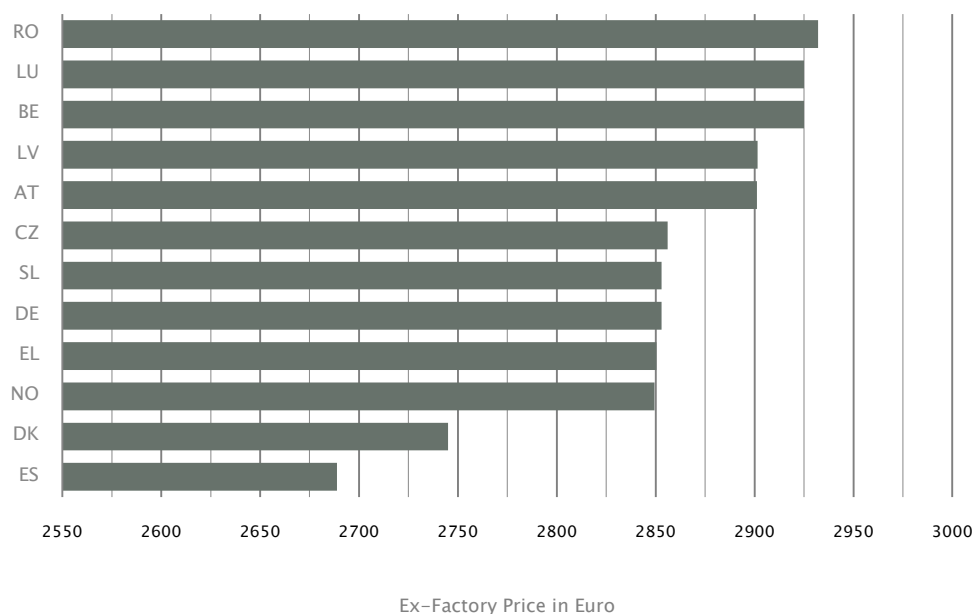
The actual price reductions achieved, however, strongly depend on the existence of alternative medicines. It is unlikely that discounts or rebates are granted for orphan medicinal products without generic competition or alternatives on ATC-4 level. Especially for orphans – which account for increasing shares of hospital budgets – the procurement process deserves special attention. Looking at the price of orphans, it becomes obvious that their prices are much higher than those of medicines used for common diseases (cf. the example of Elaprase (INN: idursulfase), an orphan used for the treatment of Mucopolysaccharidoses type II in figure 4.1).⁴⁰

³⁹ Cf. PHIS 2010a

⁴⁰ More price examples can be found in the EMINET orphan medicines Report 2009, cf. www.emi-net.eu

Figure 4.1:

Ex-Factory Price of Elaprase (INN: Idursulfase) in Euro, in 12 European Countries as of September 2010



Source: PPI 2010

The procurement mechanism of orphans depends on the place of use, thus varying for orphan medicines used for out-patients and for those used for in-patients. Different countries may use the same orphan medicine in different treatment settings (e.g. hospital use, home treatment, out-patient use, etc.). Patient with Pompe's disease in the UK can, for instance, receive Myozyme also in out-patient or home treatment after receiving initial treatment in a CoE. Such examples may influence the procurement process as community pharmacies could start dispensing such products. This is the case for Tracleer or Glivec in Germany, Austria, Belgium, Finland and France.

Considering the potential relevance the procurement process can have for the price of the orphan medicine, the following section aims to provide an overview of different procurement policies applied for orphan medicines throughout the EU.

Pharmaceutical procurement is a complex process involving many steps and a range of different stakeholders. It is strongly influenced by national and institutional policies, processes, regulations, and structures which may all contribute to the overall efficiency (hinder or support) of the procurement process.

An effective procurement process at any level must ensure that four strategic objectives are achieved:

- » the procurement of the most cost effective medicines in the right quantity,
- » the selection of reliable suppliers of high-quality products,
- » the selection of procurement and distribution systems which ensure timely and undisturbed deliveries ⁴¹

The vast majority of Member States the procurement process for orphan medicines in CoE was comparable or the identical to the one employed for all other medicines procured by hospitals. Yet a number of specific national regulations and policies exist which influence the purchasing of orphans.

In the context of procuring medicines also the supply chain of medicines is of importance. The supply chain describes the steps involved when delivering medicines to CoE (transport, storage, etc.). This process varies depending on the manufacturer and the type of product. Two main types of supply channels apply: the delivery can either be undertaken directly by the manufacturer or his agent (this is the case for Myozyme in the majority of the EU countries) or by wholesalers. In some countries (e.g., AT, LT, PT, and UK) also community pharmacies provide hospitals with certain medicines. Parallel traders only play a minor role in the provision of orphans to hospitals or Centres of Expertise respectively.

Hospital pharmacies play a vital role in the procurement of orphans as they are the main providers of medicines for in-patients. Hospital pharmacies can either act as purchasing bodies for CoE located in hospitals or as suppliers for other CoE which are not attached to an own hospital pharmacy. CoE without a hospital pharmacy often run so called “pharmaceutical depots” and rely on larger hospitals with hospital pharmacies or in some cases on community pharmacies in order to secure their pharmaceutical supplies.

4.4.2 Purchasing policies of Centers of Expertise

Three main policies (procurement tools) for CoE purchasing orphan medicines can be distinguished: Tenders, negotiations between buyer and seller or direct purchasing. As the majority of orphan medicines are monopoly products with just one marketing authorisation holder the leverage for negotiations is limited. Exemptions are rare diseases for which several treatment options (e.g. medication vs. surgical interventions, competing medicines on ATC-4 level) exist or options the distribution chain

⁴¹ Cf. PHIS 2010b

offers (e.g. one contract with one wholesaler to deliver all medicines used in the hospital department).

Tenders are by definition “...any formal and competitive procurement procedure through which tenders/offers are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous”.⁴² The public procurement of goods is regulated by the EU Directive 2004/18/EC which has been transposed into national law in all MS. Tendering can be executed openly or in restricted form. An open tender invites offers from potential manufacturers or suppliers. In practice open tenders address mainly possible suppliers (wholesalers in the case of orphan medicines with market exclusivity). The second way of tendering, called restricted tender, is open to suppliers who meet certain qualifications. Following an initial evaluation and selection of any potential suppliers, its main advantage is the limited transaction cost and the assurance of a certain level of quality.

Another way of procurement is conventional negotiations between purchaser and manufacturer or supplier (e.g. wholesaler). If the negotiation involves more than one potential supplier in order to obtain several estimates of costs or delivery options, the process is called competitive negotiation. Due to the limits imposed by the market exclusivity this procurement strategy is rarely applied for orphans. The process is called direct purchasing (cf. Figure 4.2) if a hospital purchases orphans at quoted (list) prices directly from the seller without obtaining any discounts or rebates. This strategy is likely to result in high prices for the hospital.

⁴² PHIS Glossary 2010b

4.4.3 Mapping of European purchasing processes of orphan medicines in Centres of Expertise

Most Member States apply a mix of the above mentioned purchasing policies for orphans, depending on the type of product as well as the manufacturer policies. To avoid that every hospital purchases its medicines individually, some countries have established joint purchasing bodies. These aim to centralise the procurement process and to increase bargaining power. National price regulations usually only affect maximum list prices, meaning the real price paid by the hospital is often lower. The extent of price reductions which can be achieved by the application of different purchasing strategies differs considerably, ranging from above 0% to 100% among the Member States for “normal/common” medicines.⁴³

In the case of orphan medicines the chance of receiving discounts, whether in kind or in cash, depends on the existence of alternative treatment options, e.g. on ATC-4 level. Reductions may be also achieved in the form of commercial discounts (price reductions under specific conditions), rebates (retrospective price reductions following the transaction), bundling (offering bundles of different products for one negotiated price) or cost-free products (free of charge), sometimes declared as donations).

For hospitals being a member of a joint purchasing body often results in obtaining lower prices. Through the concentration of the purchasing power the position on the market is strengthened, which can be vital especially for small hospitals. Joint purchasing bodies represent a counterbalance to monopoly providers of medicines.

In practice three different forms of purchasing mechanisms are applied in Europe:

- » Purchasing is undertaken at a centralised level through e.g. the Ministry of Health or a national (regional) purchasing agency
- » Purchasing groups operating at a regional (district or county) level, e.g. through hospital groups
- » Procurement is undertaken directly by a hospital (or its pharmacy)

Many countries use these forms in parallel, meaning that a hospital can be part of a purchasing group and procure a number of medicines through this group whilst at the same time also acquiring other medicines directly from a wholesaler or a distributor. The CoE itself never purchases medicines (incl. orphans) but requests the (joint) hospital purchasing body, sometimes together with the hospital pharmacy, to acquire them.

⁴³ Cf. PHIS 2010

Figure 4.2 provides an overview of the **three most common purchasing strategies of hospitals and their affiliated CoE** applied in Europe. Starting point of the flowchart is the Centre of Expertise which is usually located in a (university) hospital or is attached to a hospital in the form of a specialised department. If the hospital runs a hospital pharmacy, the pharmacy can act as purchasing body, meaning that it takes a leading role in the procurement process.

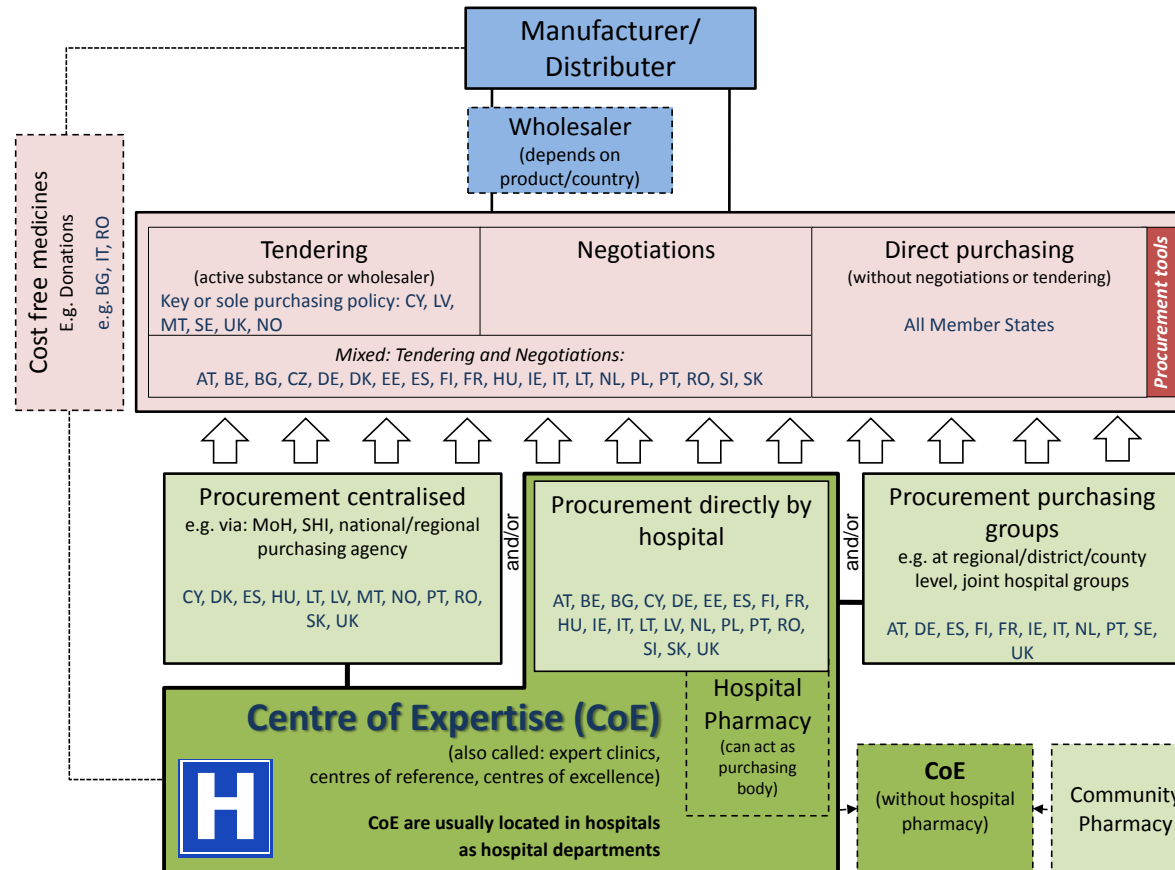
The EMINet survey 2010 showed that two main procurement tools are applied (concurrently) in Europe, regardless of whether the procurement was undertaken at a centralised level or initiated directly by the individual hospital: Tenders and negotiations. Tendering is the key purchasing strategy in eight countries (CY, EE, IT, LV, MT, NO, SE, and the UK) in case the criteria for tendering are met (cf. section 4.4.2). In Belgium, hospitals purchase orphans directly from manufacturers and try to negotiate the prices if alternative therapeutic options are available.

Under specific circumstances (e.g. in the case of compassionate use) all MS use the way of direct purchasing through the hospital, i.e. acquiring the orphan products needed directly from the manufacturer or wholesaler at quoted list prices. Sometimes direct procurement also takes place at a centralised level, for instance through purchasing agencies or joint hospital purchasing groups. The latter option is the most common.

Tendering is normally carried out by national or regional public institution such as the Ministry of Health, SHI institutions or special procurement agencies (e.g. in DK or NO). Several countries have established regional procurement committees. This is for example the case in Italy where so called Regional Therapeutic Committees have been formed. In Finland the joint municipal authorities for primary health care are responsible for purchasing medicines in hospitals. In addition, hospitals in the same region may also form purchasing groups in order to strengthen their bargaining power (e.g. in AT and NL).

In Finland the dominant purchasing process for orphans used in Centres of Expertise is a mix of tendering and negotiation. In certain cases, however, also the direct pharmacy route is possible. Examples are Fabrazyme (for the treatment of Fabry's disease) and Tracleer for which home treatment is feasible for selected patients. In these cases the products can be purchased directly from any community pharmacy.

Figure 4.2: Purchasing process for orphan medicines in Centres of Expertise (CoE) 2010



Source: EMINET 2010

In Malta and Cyprus the dominant process for all orphan medicines is tendering. As all medicines in the public market are purchased by a centralised procurement body, the hospital pharmacy never acts as a purchaser. Another form of acquiring orphan medicines is the delivery of cost free medicines (e.g. donations by the manufacturing companies). This type of procurement is voluntary and depends on the willingness of the company. Cost free medicine deliveries are difficult to analyse as barely any information is publicly available. Moreover the delivery of cost free medicines is illegal in a number of MS (e.g. DE, DK, HU, LT, and UK).

Bargaining power and hence the amount of price reductions achieved differ depending on the form of procurement and the purchasing tools applied. The amount of price reductions obtained also varies considerably with regard to the type of the product or its therapeutic class. If only one on-patent product is available price reductions are less likely (market-exclusivity). This is true for the vast majority of orphan products. This fact challenges the advantages of joint purchasing mechanisms for orphans unless market exclusivity expires. The absence of treatment alternatives for the majority of diseases treated by orphans on the European market weakens the negotiation position of purchasers further.

Price reductions granted to CoE in the European countries are voluntary (commercial discounts / rebates) in most countries. It is, however, possible that manufacturers are obliged by law to grant price reductions to hospitals or CoE respectively. This is e.g. the case in Italy where pharmaceutical companies have to provide discounts of 50% to the National Health Service when supplying orphans to public hospitals.⁴⁴

Purchasing of orphan products is not limited to CoE which are primarily responsible for diagnosis and prescription approval. For instance in France any hospital with or without a CoE (hospital pharmacies acting as purchasing body) is allowed to purchase orphans for in- or out-patients. Orphans can, in several cases (e.g. Glivec), even be purchased in community pharmacies.

⁴⁴ Cf. PHIS 2010

5 Derogatory procedures to access orphan medicines in the European Union

Patients with rare diseases may be faced with limited access to orphan medicine. This chapter gives examples for restricted⁴⁵ availability to orphans as well as outlining any derogatory procedures⁴⁶ – procedures allowing patients to obtain such products nonetheless – existing in different European countries. In order to identify derogatory procedures in place, Member States were asked to respond to the following two questions (cf. section 2.4 on methodology, the questionnaire used in the online survey can be found in Annex 1).

- » Can patients obtain an orphan in their home country even if it is apparently not available and not included in the standard reimbursement system or schedule?
- » What are the possibilities for obtaining the required orphan medicine in another EU/EFTA country?

Typically situations in which orphans are subject to restricted availability concern:

- » Unauthorised medicines which may be available via compassionate use, off-label use or on a named patient basis
- » Authorised, by not yet commercialised or launched medicines⁴⁷
- » Products for which access involves administrative requirements⁴⁸ such as obtaining the (public) payer's prior approval, conditional prescribing, the enrolment of patients in a specific therapeutic programme, or the involvement of a specialist for the disease in question or in some countries the consultation of a CoE.
- » In some cases derogation can also result in a change of the (usual) payer for the medicine.

The use of orphans in clinical and observational studies was also mentioned by the respondents, but was not subject of the report.

⁴⁵ Unrestricted availability is defined as the inclusion of an orphan in the "regular" national reimbursement or provision framework, for instance, dispensation in (specialised) hospitals or CoE, cf. section 2.1 for definitions.

⁴⁶ In this report derogatory pricing and reimbursement procedures are defined as any regulation deviating from the general reimbursement procedure or in-patient treatment schedule applicable for medicines in a given country.

⁴⁷ Note: Commercialisation usually requires administrative clearance by the country's authorities. This may for instance result in the actual inclusion in the reimbursement system after a positive decision.

⁴⁸ Note: Administrative requirements or "hurdles" are often set up consciously, e.g. for safety reasons or because of intended utilisation priorities or preferred medical practice.

5.1 Derogatory reimbursement procedures in Europe

The following sections describe, for each country, firstly treatment options available in the respective country in case an orphan is not included in the general reimbursement or provision system, and secondly the procedure which can be followed to obtain such treatment either in the own country or, if necessary, outside the home country of the patient.

5.1.1 Austria

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 reasonable.⁴⁹ Contract physicians are entitled to prescribe all medicines included in the Austrian Reimbursement Code (EKO)⁵⁰ – 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), 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, i.e. ex-ante approval by the head physician applies. In the last three years no treatment with orphans taking place outside of

⁴⁹ Art. 133 ASVG 1955, regulating the extent of medical treatment [Art. 133 ASVG 1995; BGBl. N°. 189/1955]

⁵⁰ Art. 31.3(12) ASVG, on the publication of the Reimbursement Code EKO (Art. 31.3(12))

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 medicines due to fragmented funding responsibility. 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.

5.1.2 Belgium

The reimbursement of medicines including orphans is regulated by the Royal Decree AR 21 December 2001. In November 2010, 43 orphan medicines (including BeneFIX and several other products, which had already been authorised before EC Regulation No. 141/2002 came into effect) were listed in Chapter IV of the list of reimbursable pharmaceuticals – annex to the Royal Decree.

In Belgium the prescription and reimbursement of orphans is subject to certain conditions: Initially, before prescribing any orphan, the attending medical specialist has to obtain the approval of a medical advisor of the patient's sickness fund. The Medical Advisor can, but is not obliged to, consult the "College of Medical Doctors for Orphan Drugs" (CMDOD). By the end of 2008, 18 colleges for 18 of 31 orphans available in Belgium had been established upon decision of the Drug Reimbursement Committee.⁵¹ In practice, sickness funds have agreed to refer any request to the CMDOD, subject to availability. Individual decisions are taken on a case by case basis by the CMDOD. If the prescription is approved by the Medical Advisor no patient co-payment applies.

In addition, a derogatory procedure exists for exceptional cases, for instance when the medicinal treatment is not covered by the regular reimbursement system. The derogatory procedure is followed if certain conditions (life threatening disease; rare, expensive and non-experimental treatment; no known alternatives) apply. For such cases a Special Solidarity Fund, SFF (Fonds Spécial de Solidarité), based on AR 14 July 1994, Chapter VII, Articles 24 and 25, grants an ex-post financial compensation for several types of treatments, including non-reimbursed orphans to patients with very severe diseases.

⁵¹ KCE 2010

Applications for funding (from the Special Solidarity Fund) are made on a case-by-case basis by the medical specialist attending the patient by submitting a description of the case and describing the motivation of the application. Each case is assessed by a panel of experts who decide based on data available in the literature, international recommendations and the use of the respective orphan in other countries.

If a medicine is not yet included in the Belgian positive list, the patient may be able to benefit from a compassionate use or from medical need programs by the company. Alternatively, in case the product has already been launched but is not yet eligible, the patient can also apply for individual reimbursement through the SSF. Conditions for compassionate use or reimbursement through the SSF are clearly defined.

The SSF has a limited annual budget and the Board of Medical Superintendents of the Belgian Social Insurance RIZIV/INAMI decides on the distribution of funds as well as the amount of funds awarded. The Board is composed of the medical superintendents (or their representatives) of each sickness fund and of social insurance physicians. In case a CMDOD exists for the medicine in question, the Board of Medical Superintendents is obliged to consult it before taking its decision.

Typical examples for the use of SSF funds are 1) facilitating the off-standard use of orphan medicines (as the product is not included in the regular system) or 2) reimbursement of orphans already commercialised in Belgium but not yet included in the reimbursement system. In 2007, activities related to the funding of orphan medicines accounted for about 35% of SSF's total budget⁵². Specific examples are: the reimbursement of Remodulin (INN: treprostinil) and Ventavis (INN: Iloprost) for the treatment of pulmonary hypertension. Before Myzoyne was included in the positive list in 2007, seven patients had it reimbursed through the SSF, equating to expenses of about EUR 3.5 Mio. Another orphan which was funded by the SSF before it was included in the standard reimbursement system was Xagrid (INN: anagrelide) for the treatment of essential thrombocythemia.

The Royal Decree AR 21 December 2001, Art 96.1 and 96.2 constitutes the legal base for the reimbursement of treatments of Belgian insurees with medicines (orphan or not), imported from abroad (for instance in case of non-commercialisation in Belgium). The Royal Decree determines the process, timing and conditions of reimbursement for pharmaceutical specialities whilst the Law of 14 July 1994, Art 24 and 25 regulates cases not covered by the regular reimbursement system, i.e. those supported by the Special Solidarity Fund. Sometimes, if necessary facilities for the diagnosis and assessment of rare metabolic diseases are not available in Belgium, patients seek treat-

⁵² KCE Report 112c/2009

ment in other European countries. The treatment cost resulting thereof can be – after prior agreement of the Social Health Insurance – covered by the SSF.

5.1.3 Bulgaria

The Bulgarian Ministry of Health has adopted a law⁵³ regulating the financing of treatment for diseases not covered by mandatory health insurance (National Health Insurance Fund, NHIF) for Bulgarian citizens. The law defines the criteria, terms and conditions for subsidising medicines required for the treatment of the following groups of diseases: neoplasms, conditions after transplantation of tissues and organs, Funding originates from the state budget.⁵⁴

In June 2010, 60 orphan medicines were authorised in Europe. 18 of these were included in the Bulgarian Positive List (PDL) and another 11 orphans were reimbursed by way of derogation, namely via Regulation N° 34.⁵⁵ Orphans are included in appendices 3 and 4 (i.e. the former hospital list) of the PDL which is based on the Council of Ministers Decree N° 311/2007. This means that PDL products are provided by hospitals and reimbursed by the NHIF by 100%. Non-insured Bulgarians (around 1 million inhabitants) have to pay for their hospital treatment privately, thereby being charged so called market prices.

Expenses related to any products listed in Regulation N° 34 are covered by the state budget. These products are bought centrally, i.e. not by the NHIF but by the Ministry of Health and are fully reimbursed (100%).⁵⁶

Small shares of the dispensed orphans are cost-free products which are donated by the marketing authorisation holders.

⁵³ NHIF (Regulation N° 34/25.11.2005, SG 68/19.11.2005)

⁵⁴ Bulgarian Information Centre for Rare Diseases and Orphan Drugs, cf. www.raredis.org/modules/news/article.php?com_mode=nest&com_order=1&storyid=137 (13.11.2011)

⁵⁵ BAPES 2010

⁵⁶ PHIS 2010c

5.1.4 Czech Republic

In November 2010 30 of the 61 authorised orphans⁵⁷ were included in the general reimbursement system and distributed through so-called publicly owned S-centres. These also coordinate compassionate use.

S-centres usually offer in-patient treatment but may also operate out-patient departments (policlinics) for patients not in need of in-patient treatment, e.g. for treatment provided after the initial diagnosis of a rare disease. The body deciding which orphans are provided in S-centres is the Interface Commission for Rare Diseases (Meziresortni Komise pro Vza'cna' onem).

Patients can obtain orphan products via four different types of treatment:

- » Treatment with orphans that were granted permanent reimbursement, usually in S-centres.
- » Treatment with orphans which, due to lack of data on efficacy, were only granted temporary reimbursement (12 months with the option of two prolongations) usually taking place in an S-centre. This option is limited to very innovative medicinal products i.e. usually including orphans.
- » Treatment with orphans which have not been authorised in the Czech Republic but are available via direct import on a named patient basis or via compassionate use. Costs are covered by public health insurance, if the approval of a “head” insurance physician is obtained for the treatment or costs are included in a special therapeutic programme covered by the MoH budget or public health insurance fund.
- » In case no adequate treatment is available nationally and the technology cannot be imported from another country, the patient can apply for receiving treatment abroad with the S2 form. Prior approval of the public health insurance fund is necessary, except if any delay resulting from the approval process could lead to irrevocable danger for the patients' life (Art. 16 of the Czech Republic's Act No. 48/1997 Coll. on public health insurance).

⁵⁷ As of November 2010, further 6 orphan medicinal products were under investigation

5.1.5 Denmark

If a medicine (including orphans) is on the Danish national formulary of medicines “Medicinpriser.dk”⁵⁸ it can be marketed in Denmark, i.e. dispensed in hospitals or from a pharmacy and will be reimbursed by the public payer, the regions. In November 2010 77% of all authorised orphans were included in the national pharmaceutical formulary. Orphan medicines are in the vast majority of cases restricted to be dispensed from a hospital.

All medicines (including Orphans) dispensed at hospitals are free of charge to the patient – if dispensed from a pharmacy according to a doctor's prescription there is a regular needs-based patient co-payment (up to an annual limit of DKK 3,555.0 / EUR 476.8).⁵⁹ Social subsidies or reduced co-payments may apply to chronically or terminally ill persons. Medicines used in hospital are purchased centrally by the hospital purchasing body AMGROS which is owned by the five regions.

If a medicine (including orphans) is not on the Medicinpriser.dk, this may be because it is not authorised in Denmark (a) or it is authorised but not marketed (b). In both cases a use requires a permit from the Danish Medicines Agency (DKMA):

- » Case (a): DKMA authorises ‘compassionate use’
- » Case (b): DKMA authorises the use of a medicine which is not marketed.

The administrative procedure for authorisations of case (a) and case (b) is the same and both types of authorisation may be issued to a specific doctor for the treatment of a named patient or to a ward or outpatient clinic, so that all associated physicians may write prescriptions for that medicine. The application must specify why the patient should be treated with a medicine not marketed in Denmark and the medicine needs to be of high quality and safe to use, i.e. the risk of side effects and the nature of these side effects need to be acceptable, etc.^{60,61} Any expenses resulting thereof are also covered by the regions; patients do not need to co-pay.

⁵⁸ www.medicinpriser.dk

⁵⁹ DKMA 2011

⁶⁰ Legal bases: Danish Act no. 1180 of 12 December 2005 on medicinal products as amended by Act no. 538 of 8 June 2006, Act no. 1557 of 20 December 2006, consolidation Act no. 855 of 4 August 2008 and Act no. 534 of 17 June 2008.

⁶¹ DKMA 2010

Under Danish legislation⁶², persons with a (rare) disease or condition requiring highly specialised treatment not even offered at a Danish hospital, may, under certain conditions, be treated abroad. A person has the right to access highly specialised treatment abroad provided

- » that the person has before been examined or treated at the hospital department with the highest specialist knowledge in Denmark,
- » that the hospital department confirms the need of undergoing a recognised treatment offered abroad,
- » that the hospital department advises the Danish National Board of Health to refer the concerned person to a certain specialist department or CoE abroad, and
- » that the Danish National Board of Health authorises the referral of the aforementioned person to the recommended foreign specialist department.

If the National Board of Health authorises such a referral, the Danish Government and the person's region of residence will pay for the treatment (incl. orphans) abroad.

5.1.6 Estonia

In Estonia neither specific funding mechanisms nor specific programmes to facilitate the provision of orphan medicines for patients suffering from rare diseases are in place. No explicit list of orphans qualified for reimbursement exists⁶³ but rare diseases are included in the catalogue of described diagnostic procedures for reimbursement that can be undertaken on an out-patient or in-patient basis.

Estonia has a diagnosis-based, rather intricate reimbursement system that is run by the Estonian Health Insurance Fund, Eesti Haigekassa.⁶⁴ Coverage of costs for orphans by the Eesti Haigekassa's medicines budget may be granted, depending on the diagnosis. Criteria are not so much the incidence of the disease itself but aspects such as its severity and the mortality associated with it, also the possibility of it leading to 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 as well as the challenge of matching the needs of the patient with the financial possibilities of the

⁶² The provisions governing highly specialised treatment abroad are specified in section 25 of Danish Executive order no. 62 of 20 January 2010 on the right to hospital treatment, etc.

⁶³ Medicines used in hospitals are not included in the positive list

⁶⁴ Reimbursement rates are 50% or 75/90% or 100% combined plus fixed co-payments. Socially vulnerable persons may qualify for the "exemption" reimbursement category of 90% and children <4 years always receive 100% reimbursement without co-payment. (PPRI 2007a)

medical insurance scheme.⁶⁵ Currently two centres specialise in the diagnosis and treatment of rare diseases in Estonia, Tartu University Hospital and Tallinn Children's Hospital.⁶⁶

Scheduled treatment abroad needs to be approved ex-ante by the Eesti Haigekassa. Decisions are taken on a case-by-case basis. Depending on the situation, the orphan has to either be paid by the patient upfront (the patient is reimbursed afterwards by the Eesti Haigekassa) or is paid directly by the patient's health insurance fund.

5.1.7 France

In France (orphan) medicines may be dispensed either in out-patient or in in-patient settings with four established pharmaceutical formularies or lists:

- » The positive list ("liste des médicaments remboursables agréés aux assurés sociaux") contains medicines for out-patient care, sold by community pharmacies and reimbursed by the French social insurance. If a medicine is used in the out-patient sector, the health insurance fund in charge reimburses it according to the reimbursement rate applicable based on the products' ASMR. Reimbursement can be linked to specific prescribing conditions as it is, for instance the case for Glivec INN: imatinib mesilate) which is reimbursed for some indications whereas it is not for others. Co-payments usually apply.
- » T2A medicines: About 40% of medicines used in hospitals are integrated in the activity-based costing system (DRG) and thus covered by the hospital's budget. Orphans with this status e.g., Myozyme or Elaprase (INN: Idursulfase) may only be prescribed by a CoE or – if prescribed by another public hospital– need to be approved by the respective CoE. They are dispensed to in-patients only. In hospitals, patients do not need to co-pay for orphans consumed if the cost of intervention exceeds EUR 91.-.⁶⁷
Note: Of the countries analysed, France is the one with the highest number of CoE.
- » Liste en sus or "Non-T2A": This supplementary list details costly hospital medicines excluded from the DRG system and thus reimbursed separately by the French social insurance funds. In the beginning of 2011 around 290 active substances⁶⁸ were

⁶⁵ PPRI 2007a

⁶⁶ EUCERD 2009

⁶⁷ PHIS 2010

⁶⁸ www.codage.ext.cnamts.fr/codif/bdm_it/index_tele_ucd.php?p_site=AMELI

listed as compared to 120 in 2008⁶⁹. Products include oncologic medicines, blood products but also orphans for enzyme replacement therapies and others.

- » Liste rétrocession: Medicines on this list may be dispensed by hospital pharmacies to in- and out-patients. If dispensed to out-patients the cost is usually reimbursed by the French Social insurance, if dispensed to in-patients the cost is covered in the hospital budget. An example for orphan medicines on this list is Tracleer.

Medicines included in both, the Liste en sus and the Liste rétrocession, are always paid by the health insurance fund irrespective if they are dispensed to in- or out-patients, i.e. the Liste en sus is a derogation of the other one. Orphan medicines concerned are Vidaza (INN: azacitidine) or Zavesca (INN: Miglustat).

The idea of this supplementary financing for costly medicines is to guarantee equitable access to the most innovative pharmaceuticals which would introduce considerable variation in the distribution of DRG costs, either because of the very expensive nature of these pharmaceuticals, or because the number of patients consuming these products is marginal within the DRG. In addition, the budgetary burden of orphan medicines shall not be carried by hospitals specialising on rare diseases – in particular through their CoE – alone, but by the so-called national solidarity health coverage budget, hence guaranteeing equal access to all patients in all parts of the territory. The list is regularly updated, with new entries as innovative and expensive pharmaceuticals reach the market; in theory pharmaceuticals should be removed from this list and put back into the DRG system when they begin to be used more widely and/or their cost decreases.

The Market Authorisation Commission (AMM Commission), advised by the Transparency Commission – which is part of the National Authority for Health (“Haute Autorité de Santé”, HAS) – decides whether an orphan medicine is approved for use in primary care or rather for hospital use; if a medicine is licensed for group use, if it may be used in general practice and also in hospitals, etc. Medicines solely dispensed in hospitals are included in the so-called hospital reserve (“liste des médicaments agréés aux collectivités or réserve hospitalière”).⁷⁰

Newly authorised orphan medicines are, like any other innovative medicine, subject to an assessment by the Transparency Commission. This results in the determination of a so-called ASMR rating⁷¹ (a measure for assessing the increase in the medical benefit

⁶⁹ DREES 2008

⁷⁰ PHIS 2010b

⁷¹ The ASMR rating of a medicines plays a key role in the pricing decision taken by the Pricing Committee („Comité Economique des Produits de Santé“, CEPS).

achieved by the new therapy, compared to existing therapies). In 2009, for instance, Vidaza (INN: azacitidine) for myelodysplastic syndromes and NPlate (INN: romiplostim) for thrombocytopenic were categorised as ASMR II (=significant progress in terms of therapeutic efficacy and/or reduction in side-effects).⁷² The ASMR category is one of the criteria relevant for determining the out-patient reimbursement rate of the medicine: The better the ASMR (grading from I (best) to V (weakest), the higher the reimbursement rate.

The process by which medicines including orphans are provided without marketing authorisation, i.e. on basis of compassionate use is called “Autorisations temporaires d'utilisation”, ATU (Temporary authorisations for use). Thereby the attending (specialist) physician or CoE needs to formally apply to the French agency for health products (AFSSAPS) to approve of the treatment. The price of the product is freely determined by the manufacturer and the product is made available for the patient on a case by case basis. The cost is covered by the usual payer, the French Health Insurance Funds. As soon as the marketing authorisation is granted, the regular procedures apply and the “ATU” is no longer possible. Examples of medicines that were made available to French patients via ATU are Vidaza (INN: azacitidine) or Mozobil (INN: plerixafor).

In the course of the EMINet 2010 online survey France declared that any orphan medicines urgently needed for medicinal reasons are made available to patients in France, meaning that, under normal circumstances, no treatment abroad will be necessary.

5.1.8 Hungary

There is no specific funding for orphan products outside the general scheme, but a “earmarked” budget for selected medicines given on a “named patient basis” (not exclusively for orphan drugs). Medicines on the reimbursement list are funded by the Hungarian Health Insurance Fund OEP. Prescription is often subject to strict conditions, such as the use as second- or third-line therapy or the prescription by pre-defined medical specialist or centre, acting like CoE.⁷³

By the end of November 2010 23 orphans (counted by available packs and presentations) were included in the Hungarian positive list. With the exception of two orphan medicines used for the treatment of Fabry's disease (e.g. Replagal, INN: agalsidase

⁷² IMS 4/2010a

⁷³ IMS 4/2010b

alpha and Fabrazyme, INN: agalsidase beta) which may only be administered in hospitals, orphan are provided via out-patient care.

Orphan products not included in the positive list can be obtained via the “named patient basis system” if considered necessary by the attending medical specialist/physician. In these cases the OEP approves the claims for reimbursement individually; i.e. reimbursement is linked to the patient rather than to the medicine.

5.1.9 Ireland

The provision of medicines takes place through a number of reimbursement schedules, so-called community drug schemes, major ones being⁷⁴:

- » The **General Medical Services (GMS) Scheme** provides, free of charge, medication dispensed by a community pharmacy to persons who cannot afford such services from their own resources without undue hardship, covering around 30% of Ireland’s population including persons aged 70 years and over
- » The **Drugs Payment Scheme (DPS)** for persons who are resident in Ireland and who do not have a current medical card benefit. An individual or family has to pay no more than EUR 85 (2007) in a calendar month for approved medicines
- » Persons who suffer from one or more of a list of selected diseases are entitled to obtain, without charge, irrespective of their income, necessary medicines and/or medical appliances through the **Long Term Illness (LTI) Scheme**.
- » The **High Tech Medicinal Products (HTMP)** Scheme provides for the supply and dispensing of high-tech medicines through community pharmacies

Positive lists indicating reimbursable pharmaceuticals are in place for the GMS scheme (which is up-dated monthly) and the HTMP scheme. Examples of High-tech medicines are: interferons, ARVs, growth hormones and orphans such as Tracleer (INN: bosentan), Revatio (INN: sildenafil) or Wilzin (INN: Zinc acetate dehydrate). Medicines are purchased by the Health Service Executive (the Irish National Health Service) and supplied through community pharmacies. The patient’s primary eligibility (GMS or other scheme) determines whether co-payments apply or not.

No formal derogation from these general reimbursement schemes exists but individual hospitals may decide to supply a patient with an expensive orphan that is neither reimbursed under the community drugs schemes (GMS and HTMP) nor accessible in other schemes. This is for instance the case for Myozyme. Furthermore companies are

⁷⁴ PPRI 2007b

allowed to supply an orphan to patients free of charge to gain experience, e.g. on a compassionate use basis.

5.1.10 Italy

Patients with rare diseases may access orphan medicines through three different ways⁷⁵:

- » Authorised orphans are available via the general reimbursement scheme and the usual channels, i. e. through pharmacies or hospitals that are reimbursed by the NHS.
- » The access to unauthorised medicines with no alternative treatment or potential off-label use is regulated by Law N°. 648/96, which came into force in 1996
- » and
- » Medicines with non-approved indication, including orphans, are accessible through the AIFA fund ("Fondo AIFA 5%") stipulation.

Law N°. 648/96 enables Italian patients to gain access to innovative treatments for disorders where no alternative therapy is available. The law applies to 1) (innovative) medicines already approved in other countries but not yet in Italy, 2) to products which have demonstrated clear benefit while "under clinical investigation" and 3) for off-label use. A medicine is considered for inclusion in the 648/96 list following an application to the Italian Medicines Agency, AIFA's Technical Scientific Committee (Commissione consultiva Tecnico Scientifica, CTS) filed by physicians specialised in the treatment of the disease in question, a university or a centre of reference. The application must be supported by a scientific dossier, which is reviewed by the CTS. The Scientific Committee may add the (orphan) medicine to the list for reimbursement, under exceptional circumstances and following compelling clinical results.

A list of the more than 40 medicines, approved for treatment under this law, is published on AIFA's website⁷⁶, together with the approved indication. Orphans included are, for instance, Vidaza (INN: azacitidine), Soliris (INN: eculizumab), Elaprase (INN: idursulfase), Revlimid (INN: lenalidomide), Lysodren (INN: mitotane), Mozobil (INN: plerixafor) or Yondelis (INN: trabectedin). Medicines under law 648/96 are funded from the 45 Mio. Euro AIFA fund. In 2010 an application for inclusion in the national pricing

⁷⁵ The legal bases being the MINISTERIAL DECREE 279/2001, the LAW 648/1996 and the MINISTERIAL DECREE 11/02/1997

⁷⁶ www.agenziafarmaco.it/sites/default/files/elenco1_farmaci_l648_rev.pdf or www.agenziafarmaco.it/it/content/uso-speciale-dei-farmaci (in alphabetical order)

and reimbursement procedure was submitted by the manufacturers of Onsenal (INN: celecoxib), Mozobil, Mepact (INN: mifamurtide), Ilaris (INN: canakinumab) and Vidaza.

The aforementioned “Fondo AIFA 5%” was established with the Law No. 326/2003 and became operative in 2005. It is designed to promote orphan medicines for rare diseases and medicines awaiting market entry. When Myozyme was launched in Italy, it was added to the list of medicines eligible for this AIFA fund. Other orphan medicines reimbursed through the AIFA fund are Wilfactin for the von Willebrand disease or Diaminopiridina for the treatment of the Lambert–Eaton syndrome. By September 2010 five authorised orphans, namely Ceplene (INN: histamine dihydrochloride), Gliolan (INN: 5-aminolevulinic acid hydrochloride), Photobarr (INN: porfimer sodium), and Siklos (INN: hydroxycarbamide), which at that point in time were not marketed in Italy and therefore not included in the Italian NHS system⁷⁷ were also made available through the AIFA fund.

The Ministerial Decree 11/2/1997 allows the import of unauthorised orphans on a case-by-case basis if the attending physicians believe that the specific medicine is necessary for the patient. The usual payers for such orphan medicines are the regions except for those acquired directly by a hospital or Centre of Reference. In the latter situation orphans are also reimbursed by the Italian NHS.

5.1.11 Latvia

The “special” reimbursement of orphan medicines such as Revatio (INN: sildenafil), Nexavar (INN: sorafenib), Volibris (INN: ambrisentan) or Wilzin (INN: zinc acetate dehydrate) is based on the regulation of the Cabinet of Ministers No. 899 on Procedures for the Reimbursement of Pharmaceuticals and Medical Devices for Ambulatory Care as of 31 October 2006. It stipulates the following requirements: After an individual application for one patient with a given indication a doctors’ advisory committee (consilium) can approve the use of the orphan. However, a budgetary ceiling of LVL 10,000 (~ EUR 14,000) is imposed on each patient. If the patient exceeds this limit for a period of 12 months s/he has to pay the remaining amount out-of-pocket.

⁷⁷ The marketing authorisation holders had not submitted a national pricing and reimbursement request.

5.1.12 Malta

In Malta no formal derogation from the general provision system (national formulary) is in place. A patient may however also obtain an orphan product through the Exceptional Medicinal Treatment Policy (EMTP). This policy is intended to provide high quality and cost-effective treatment that meets individual patient needs based on the assessment of available research evidence and effective clinical outcomes.

Through EMTP, medicinal treatment not covered by National Medicines Formulary, for instance treatment of a new, novel or exceptional nature (including orphan medicines), is still provided to the patient. A specialist files an individual application and the request is sent to the Directorate of Pharmaceutical Policy and Monitoring where the reviewer (pharmacist) compiles a summary of the patient's case. Information about the condition, treatment and costs involved is presented in the summary. The Director of Pharmaceutical Policy and Monitoring reviews the request and case profile and decides whether or not to approve the medicine. If the medicine is approved it is bought on a named-patient basis.

5.1.13 Norway

Norwegian reimbursement decisions are, to a large extent, based on proven cost effectiveness, which is sometimes difficult to achieve for orphan medicines because of the small target patient group.

If a medicine is not eligible for the so-called "automatic" reimbursement, i.e. the general reimbursement scheme, it still may be reimbursed following the approval of an individual application filed by the attending physician. In such situations some evidence needs to be presented, showing that the product can be used for the indication in question. No evidence of cost effectiveness has to be provided. Individual reimbursement will not be granted if the treatment is experimental or the degree of evidence is too low. The national regulations on the reimbursement of medicines (Art. 3, "Blåreseptforskriften") constitute the legal basis for these provisions.⁷⁸

The payer of medicines, including orphans, is always the National Insurance Administration.

⁷⁸ www.lovdata.no/for/sf/ho/to-20070628-0814-0.html#3

5.1.14 Poland

The provision of orphans takes mainly place in the frame of therapeutic programmes. Such programmes are separately contracted to providers by the National Health Fund and operate on a “named” patient basis. The largest programme currently covers 7,500 patients. Altogether, the annual expenditure for therapeutic programmes amounted to PLN 1.09 billion / EUR 273 million in 2009.⁷⁹ To receive non-standard oncology treatment with orphans like Nexavar (INN: sorafenib), Sprycel (INN: dasatinib) or Glivec (INN: imatinib) or enzyme replacement therapy attaining medical specialists need to seek prior consent of the regional branch director of the Polish National Health Fund for their patients. A regional counsellor of the National Health Fund and the so-called “hospital qualification team” of the centre where the treatment will take place need to approve the treatment as well.

For medicines, including orphans not eligible for general reimbursement patients first need to pay out-of pocket but may apply to the President of the National Health Fund for “special” reimbursement. According to Polish Pricing and Reimbursement authorities a common situation is that such an application is submitted together with a direct import application in case the product is not (yet) launched. The President of the National Health Fund decides on reimbursement on a “named-patient basis” depending on existing funds and a number of other criteria (e.g., if the product is authorised in another country and was not explicitly denied marketing authorisation in Poland, if it is necessary to save the patient's life, and if there is no other medicine with the same active ingredient marketed in Poland unless it has the same price). The import application needs to be submitted by the treating specialist physician or the treating hospitals and is evaluated by the MoH with the assistance of a specialist in this field of medicine.⁸⁰

Regarding treatment abroad, the President of the National Health Fund may permit on case-by-case basis to fund treatment (including any travel and accommodation cost) for therapies that are necessary to save the life of a patient and which is unavailable in Poland. The decision follows an application submitted by the patient or his/her spouse which has to be approved by a treating physician and a consultant in the corresponding field of medicine. Such a situation, however, has not occurred for an orphan so far as medicines are rather imported on such occasions.⁸¹

⁷⁹ IMS 10/2010, p. 11

⁸⁰ Polish Pharmaceutical Law of 6 September 2001, Art. 4

⁸¹ Art. 26 of the Polish Act of 27 August 2004 on health care services financed from public funds (Journal of Laws 2008, No. 164 item 1027)

5.1.15 Portugal

The funding of orphan medicinal treatment in the Portuguese NHS system depends on the place of use that can be out- or in-patient. Authorised orphans used in out-patient treatment (e.g., Glivec) and dispensed by pharmacies are the responsibility of the Portuguese Medicines Agency INFARMED, whereas orphans used in hospitals are paid from the hospital budget. Public hospitals are funded through a diagnosis related payment system and hospital admission charges.

Based on the Portuguese National Rare Disease Plan the reimbursement of orphan medicines may be linked to conditions such as the obligation to enrol in a registry: this is for instance the case for Myozyme. The treatment of Morbus Pompe patients with Myozyme needs to be approved and monitored by the National Coordination Centre (a Commission nominated by Minister's decree).

If an authorised (orphan) medicine is not commercialised in Portugal but is marketed in another Member State the treating hospital (CoE) can submit a request for special authorisation explaining the reasons for the request to INFARMED via specific forms. If INFARMED approves the use, the hospital acquires the medicine directly from the manufacturers. The payer is the NHS, administrated by the Central Administration of the Health System and the regions through the diagnosis-related payment system. There is no co-payment requested from the patient. Examples where this has been the case are medicines for the treatment of myelodysplastic syndromes, rare ovarian cancer or Wilson's disease, a genetic disorder that prevents the body from getting rid of extra copper.⁸²

5.1.16 Romania

In October 2010, 18 authorised orphan medicines (e.g. Tracleer, Myozyme and other enzyme replacement therapies) were available and mainly dispensed in hospitals. For some orphans the enrolment of the patient in a specific health programmes is mandatory. In addition, it is possible to grant a temporary use licence to treat patients in Romania with non-available medicines, whether authorised or not (i.e. compassionate use). However, in such cases the public payer will not reimburse the orphan product.

It is possible for patients to receive any kind of treatment abroad, whereby treatment with orphan medicines is not considered as particular situation. Applications for

⁸² Portuguese Decree-Law No. 176/2006, 30 August 2006

treatment outside Romania are decided case-by-case. There is an ear-marked health care budget for treatment abroad available.

5.1.17 Slovak Republic

To obtain a non-authorised or non-reimbursed orphan medicine the treating specialist physician needs to apply to the insurance fund in charge of the patient in case of out-patient care or at the Minister of Health directly. In addition, the local committee for rational drug therapy or the appropriate ethical committee needs to endorse the application.

If the treatment occurs in a hospital or a CoE the medicine is covered by the hospital budget otherwise the respective insurance fund has to pay. Diseases for which the use has been approved are phenylketonuria, Fabry's disease, Gaucher's disease, and also Myozyme for Pompe's disease. It is also possible to access orphan medicines via compassionate use programmes.

5.1.18 Spain

The majority of authorised orphans is marketed in Spain and included in the National Health System formulary, thus being eligible for full reimbursement.⁸³ In some autonomous regions the regional governments have established protocols and patient management schemes as pre-requisites for access. Some orphans are reserved for use in hospitals and CoE, respectively. Orphans used in an out-patient setting need to be prescribed by a specialist for the rare disease.

For un-authorised (orphan) medicines or for off-label use the following regulations apply:

4. Compassionate use for medicines under investigation for patients with a chronic or life-threatening disease that are not able to be treated satisfactory with an authorised medicine (based on Regulation (EC) No 726/2004):
 - a) Authorisation for individualised access: The treating hospital needs to submit a separate application for a individual patient to the Spanish Medicines Agency accompanied by a dossier containing the hospital medical director's conformity, the prescriber's clinical report justifying the clinical need for treatment, if

⁸³ 87% in 2009, according to EUCERD 2009

- applicable the sponsor's conformity, the number of packages required and the patient's written consent.
- b) Temporary Use Authorisation of medicines under investigation: The Spanish Medicines Agency will be able to set up a resolution for Temporary Use Authorisation of medicines under investigation independent of a clinical trial for medicines which are in an advanced phase of clinical investigation as long as the use is for a significant group of patients. The Temporary Use Authorisation will include all the conditions and requirements for using.
5. Access to medicines in different conditions to those authorised ('off-label'), based on Act 29/2006 for Guarantees and the Rational Use of Medicines and Healthcare Products, Art. 24 "Guarantees for the availability of medicines in special situations": The use of medicines for other indications to those established in the Product Characteristics Summary will be exceptional and limited to those situations with a lack of therapeutic alternatives for a patient. The physician must justify the need for the use of the orphan medicines and inform the patient about potential risks and benefits and obtain his/her written consent.
 6. Medicines not authorised in Spain but in other countries as stipulated in Royal Decree 1015/2009 of 19 June 2009 for the availability of medicines in special situations: The Spanish Medicines Agency will authorise exceptionally the access to medicines not authorised in Spain whenever the following conditions exist:
 - a) No medicine is authorised (or being authorised and not marketed) with the same composition or the available dosage and/or pack does not allow an appropriate treatment.
 - b) There is no authorised medicine that represents an adequate alternative for that patient available in Spain.
 7. Any application needs to be accompanied by the prescriber's clinical report that justifies the clinical need for treatment and the estimated treatment duration, the number of packages required, scientific documentation for using, patient's written consent and the sponsor's conformity, if necessary. The Spanish Medicines Agency will make protocols for using medicines not authorised in Spain when there is a need concerning a significant subpopulation of patients.

The payer for all three described situations is the National Health Service, but in some case the companies act as "sponsors". Examples of orphan medicines made available to patients by one of the explained derogations are: Diacomit (INN: stiripentol), Mozobil (INN: plerixafor) as well as Gliolan (INN: aminolevulinic acid) and Ilaris (INN: canakinumab), the two latter during their reimbursement evaluation.

5.1.19 Sweden

If an authorised or unauthorised orphan medicine is not available in the general out-patient reimbursement scheme, the cost of the medicines can nonetheless be covered by the public payer. Medicines eligible for general reimbursement need to demonstrate their therapeutic value and need to have a reasonable price. The decision is taken by the Dental and Pharmaceutical Benefits Board (TLV).

To obtain reimbursement the treating specialist physician has to apply for the patient in need. To obtain approval the treatment has to be considered as cost-effective for the individual patient. If approved the (orphan) medicine is provided for one year (so-called named patient prescription). The payer is in both cases, general and individual reimbursement, the county, but in the latter case the counties decide on a case-by-case base. Medicines not included in the general reimbursement scheme for which such exemptions have been granted were Kuvan (INN: sapropterin hydrochloride) and Elaprase (INN: idursulfase).

Orphans used in hospitals and not included in the hospital formulary are subject to case-by-case decision on hospital or county level. As a consequence accessibility of orphans varies between counties. Due to the unequal distribution of patient there is a solidarity funding between the county councils in place for two Rare Diseases (Gaucher's Disease and haemophilias). There is a number of CoE established in Sweden such as a Rett syndrome centre, four cystic fibrosis centres, a porphyry centre and a centre for children with congenital malformations and syndromes.⁸⁴

5.1.20 United Kingdom

All authorised (orphan) medicines are principally available in the British National Health Service (NHS) with moderate (out-patient care) or no patient co-payments (in hospital care).⁸⁵ Orphans, like other medicines, are dispensed by hospital pharmacies and specialist centres. Home delivery is available for various products, for example enzyme replacement therapies like Myozyme. Patients with rare diseases can receive unlicensed

⁸⁴ EUCERD 2009

⁸⁵ The British pharmaceutical system does not feature a "positive list" like many other countries do and no orphan medicine is included in the so-called "black" list (Schedule 10 to the NHS (General Medical Services) Regulations 1992 list drugs and other substances not to be prescribed under the NHS pharmaceutical services), the most recent version always to be found in part XVIII A of the Drug tariff (www.ppa.org.uk/edt/January_2011b/mindex.htm)

orphans; in such cases the treating physician applies to the British Medicines Agency MHRA to import it on an individual named patient basis.

Accessibility to medicines including orphans is generally determined by the National Institute for Clinical Excellence (NICE). But as orphans target small populations NICE, in principle, accepts higher uncertainty around the clinical and cost effectiveness evidence of these treatments compared to those for more common diseases.

One of the mentioned exemptions concern so-called “ultra-orphans”⁸⁶: These are not subject to NICE appraisals but are dealt by the National Commissioning Group (NCG). The NCG is a standing committee of the National Specialised Commissioning Group that organises “specialised services” on a central level.

Any application of a patient together with his physician for a treatment with ultra-orphans as well as for other rare specialised services is referred to the NCG for assessment by clinicians. The NCG evaluates the application received from the clinician, mainly based on clinical desirability. Although there is an implicit examination of costs associated with services, cost effectiveness or opportunity costs are not criteria used to reach decisions. This is often criticised by fund-holding regional Primary Care Trusts (PCTs), as it seems that these specialised services are protected from the more rigorous assessments (such as the NICE process) that other health technologies have to undergo. For other orphans decisions are taken by relevant funding bodies at PCT level, not nationally, in the light of available funds. The NCG funds certain orphans at national level – also medicines not funded locally by PCTs. This has led to the fact that the availability of an orphan could vary throughout the country, depending on the place of residence of a patient. In addition, the Scottish Medicines Consortium, that has a similar role to NICE, can decide on the access to orphans for Scottish residents.

An OHE report of 2009 explains that in cases where new orphans have not been evaluated by NICE or have been rejected for use in the NHS, and have not been referred to the NCG or, in Scotland to the Scottish Medicines Council, treating clinicians have to request funding on a case-by-case base directly from the PCT. These PCTs treat each request as a special case and can approve the reimbursement based on the so-called “exceptional circumstances”. The process is claimed to be resource-intensive, as it involves panel decisions from a number of clinicians and managers and does not ensure consistency across different areas of the country.⁸⁷

Regarding treatment abroad, responsibility for any approvals is devolved to the local PCT. Patients can access any health care service in another MS that is the same as or

⁸⁶ Orphan medicines that target diseases with a prevalence of less than one in 50,000 inhabitants.

⁸⁷ OHE 2009, p. 11f.

equivalent to a service that would have been provided to the patient under the British NHS. The patient then has a right to claim reimbursement up to the amount that the treatment would cost had the patient obtained that treatment from the NHS – or the actual amount where this is lower. The principal considerations for judging whether a treatment is reimbursable are 1) whether there is a proven clinical need for the treatment and 2) whether the patient would have been entitled to the same or similar treatment on the NHS.

5.2 Treatment options for patients in their home country in case of non-availability

13 out of the 22 countries responding to the EMINet 2010 survey (AT, BE, CZ, DK, ES, FR, IT, LV, PL, PT, SK, SE and NO) explicitly stated that it is possible for a patient to obtain an orphan medicine even it is basically not available, i. e. included in the general reimbursement system in their country (cf. section 2.1 for definitions).

Five respondents (FI, IE, MT, SK and RO) declared that this was not possible and three MS did not reply to this question. The UK commented that, in principle, all (orphan) medicines are included in their National Health Service (cf. section 5.1.20).

Derogatory reimbursement regulations mentioned most frequently in case of non-availability of an orphan in a country concerned “compassionate use”. Compassionate use is regulated in Council Regulation 726/2004, Art. 83⁸⁸ and allows the use of non-authorised medicines if the product is imported in line with national rules stipulates and is dispensed directly to defined patients (“named patient use”) or patient groups (“cohort use”) under limited and exceptional conditions (cf. section 2.1). It is important to mention that compassionate use is also possible for medicines without an orphan designation – actually all derogations mentioned by the Member States were applicable without differentiation for “regular” medicines and orphan products likewise.

Besides compassionate use there are two further options to use un-authorised orphan medicinal products in a country, 1) in clinical trials and 2) via off-label use like the utilisation of Viagra instead of the orphan Revatio (both containing sildenafil) for the treatment of PAH. Yet, the latter two options were not explicitly investigated in the EMINet survey among Member States.

⁸⁸ REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:EN:PDF>

A number of countries have established (additional) administrative requirements⁸⁹ to obtain orphans not included in the general in- or out-patient provision system:

The most frequent are 1) prior approval from the public payer (e.g., AT, BE, DK, PL, UK) and 2) that the dispensing of the orphan medicine had to take place in a specialist centre or CoE for the rare disease or that at least the prescription needed to be discussed with a medical specialist at the centre (e.g., FR, IT, CZ).

Conditional prescribing – that can take various forms – is also quite common in the reimbursement of authorised orphans in Europe. Possible forms include:

- » Access only for specific indications, especially for orphans with more than one designation such as Glivec (e.g., AT, BE, FR)
- » Access only for patients with defined diseases (e.g., EE)
- » Access as second- or third-line therapy (e.g., AT, BE, HU, SE)

Different payer: Belgium, Bulgaria, Italy, Latvia and Lithuania explained that in their countries the use of orphan medicines could also be covered by a specific fund like the “Fondo AIFA 5%” in Italy (cf. section 0) or the Special Solidarity Fund in Belgium (cf. section 5.1.2).

In a few countries patients need to enrol in patient registries (for instance Morbus Pompe patients in Italy and Portugal) or need to be included in therapeutic programmes (e.g., CZ, PL, RO) to obtain (medicinal) treatment for a number of rare diseases.

It is important to note that the derogatory procedures described above do not necessarily apply for all orphans in the country and that in some cases a combination of the policies is in place.

⁸⁹ Note: Administrative requirements or “hurdles” are often set up consciously, e.g. for safety reasons or because of intended utilisation priorities or preferred medical practice.

5.3 Treatment options for patients in foreign EU/EFTA countries

The access to medical treatment including the necessary medicines in another EU/EFTA country than a person's country of origin is laid down in Regulation EEC No. 1408/71 of the Council of 14 June 1971 on the application of social security schemes to employed persons and their families moving within the Community.⁹⁰ It stipulates that persons residing in another Member State as their own are subject to the same rules as national insured persons and are qualified for the same benefits. This Regulation is accompanied by implementing Regulation EEC No. 574/72 which covers its practical execution (competent national authorities, administrative formalities, etc.).

However, the research focus was not patients in need for a specific orphan medicine who are residents of other EU countries but patients that, for whatever reasons, could not obtain this medicine in their home country. Additional important set of laws are EC Regulations 883/2004 and 897/2009 that, together with the Cross-border health care directive⁹¹ outlines the rules for patients with rare diseases who seek treatment with orphan medicines not available or accessible in their home countries.

According to EU legislation patients are entitled to receive “scheduled” medicinal treatment in another EU/EFTA country than their own

- » if the treatment is covered by their (statutory) health insurance / national health service but not available in their home country or
- » if the treatment might not be received timely under given medical circumstances (i.e. would cause additional pain, would affect the probable course of the disease negatively or would increase the nature of disability).

In case of a non-emergency hospital treatment abroad prior approval from the national sickness fund or National Health is mandatory⁹² to ensure that patients do not have to pay their treatment including necessary medicines out-of-pocket. The Council directive on patients rights in cross-border health care states that in future prior approval by the national third party payer could also be needed for out-patient health care that requires a highly specialised and cost-intensive medical infrastructure. To consult a CoE in another EU country or to have an orphan medicine prescribed and dispensed there, prior approval of the national payer is thus mandatory.

⁹⁰ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1971R1408:20070102:EN:PDF>

⁹¹ European Parliament 2011

⁹² Approval is proven by presenting a completed S2 form to the provider of the service in an EU or EFTA country.

Despite these regulations we learned from the EMINet survey that the medicinal treatment of rare diseases rarely takes place in other than the patient's home country. No country could give an example of an orphan where this has actually happened lately and some, such as Romania, stated that treatment with orphan medicines was not seen as a particular situation.

Eleven responding countries (ES, FI, FR, IE, IT, MT, NO, RO, SI, SK, and UK) affirmed that their national pharmaceutical system did not foresee any explicit derogation regarding the treatment of their patients with orphan products in another country. The main reason given, e.g. by FR, IT, ES, NO or SK was that an orphan not included in the national reimbursement system or not available at all was rather imported than having the patient receiving the treatment in another country. In such cases mostly the same reimbursement rules were valid, e.g. individual application by the attaining medical specialist or the approval of a social insurance specialist in the case of derogatory national reimbursement. France declared that any orphan really needed for medicinal reasons was accessible in the country.

Of the remaining countries four did not reply to the question and seven countries (AT, BE, CZ, DK, EE, LV and PL) said that explicit derogatory procedures were established to arrange treatment in another Member State. Nevertheless, the procedure predominantly concerned genetic testing and other diagnostic procedures.

The role of specialised CoE abroad was not stressed by any of the responding 22 countries. The only replying CoE that reported at least a couple of patients from Austria, Greece and Croatia was the "Villa metabolic" at the Medical University Mainz in Germany. However, their biochemical laboratory examined probes from patients but did not actually treat them. Another CoE for PAH in Spain reported that they have in average 1–3 foreign patients for diagnosis per year and the Polish CoE for Pompe's disease, the Children's Memorial Health Institute had two foreign patients.

Summarising, most CoE stated that treatment is possible with form E112 (none of the interviewed was aware that this form was substituted by form S2 in the mean time) but could involve "complex paper work". An Austrian clinician who had diagnosed a patient from Italy with a rare disease (although neither PAH nor Morbus Pompe) explained that in addition to the form E112 the owner of the Austrian hospital also had to approve the treatment of the patient before the centre was allowed to start with testing and diagnosis.

6 Conclusions and lessons learned

The present report is part of an initial investigation to assess the feasibility of creating a coordinated system to access orphan medicines in Europe.

Regarding the availability and access to orphan medicines (briefly: orphans) the authors

- » focused on the reimbursement and the purchasing process of orphan medicines in Member States, especially in already established national Centres of Expertise (CoE) and
- » explored any existing derogatory procedures for patients to obtain orphans outside the “regular” national reimbursement framework

6.1 Access to orphan medicines in Europe

In previous years patient interest groups such as for instance EURORDIS⁹³ reported heterogeneous availability of orphan medicines in Europe, arguing that the ways of accessing such medicines showed considerable regional variation.

The present report shows that the availability situation has not changed much since the 2007 EURORDIS report: Only ten of 22 countries participating in the EMINet 2010 survey declared that publicly funded access to orphan medicines was always granted if needed. Six of the ten countries (AT, BE, CZ, FR, HU and SE) stated that access was linked to specific conditions such as needing to obtain approval for the initial prescription by a centre of reference (e.g. in France) or by a “head physician” of social insurance (e.g., in Austria or Belgium). In Finland this is the case only for Fabry disease, where all patients are referred to one university hospital and treatment commences when pre-set diagnostic criteria are met.

Five responding countries (EE, LV, LT, PL, and RO) acknowledged that access was limited due to budgetary constraints; Slovenia commented that coverage/reimbursement for some of the most expensive treatments were not always guaranteed. Regardless of limited budgets, none of the 22 surveyed countries have patients pay their orphans mainly out-of pocket.

⁹³ EURORDIS 2007

It also became clear that access to orphans is not only heterogeneous in the different Member States but that different models/approaches also exist within the individual countries (e.g. UK, SE). This is due to the large diversity of rare diseases and the therapies applied. It is assumed that also in the future, different ways of dispensing orphan products will continue to exist.

The detailed survey undertaken for two selected orphans, Tracleer and Myozyme, showed, that even the same medicine was dispensed very differently in the different Member States: Tracleer is, for instance, sold in public pharmacies and reimbursed by the sickness funds in Germany and is even used out-patient in Finland, but is dispensed on a “named patient” basis in Poland or is dispensed through hospitals (in in-patient and out-patient departments) in France.

A patient with Pompe’s disease may receive treatment with Myozyme on an out-patient basis or even at home after undergoing initial treatment in a CoE in the UK, whereas Myozyme is considered a hospital-only product in most other countries (e.g., France). In Italy and Portugal patients need to be enlisted in a registry in order to receive reimbursement for Myozyme.

6.2 Centres of Expertise and purchasing procedures for orphan medicines

Despite all efforts of Orphanet and EURORDIS first within the EU initiatives such as the EU High Level Group on Health & Medical Services / WG European Networks and Centres of Expertise, and thereafter in the DG SANCO Rare Disease Task Force and now the EUCERD, many national stakeholders are still unfamiliar with the concept of Centres of Expertise leading to the fact that many Member States do not have any official CoE established nor do have started the process of identifying and designating CoE (in a legal framework). Perhaps this process will be boosted when all MS have developed a national plan on rare diseases until 2013 as it is recommended by the Council of Europe.⁹⁴ So far, six countries (BG, DK, FR, IT, ES and SE) have national plans.

The number of identified CoE for the two examined rare diseases, PAH and Morbus Pompe differs considerably per country, and does sometimes not correspond to the size of the country or the number of patients concerned. This may be due to the aforementioned lack of common understanding and national plans. France, for in-

⁹⁴ Council of the European Union 2009

stance, lists 71 CoE for Pompe's disease in the Orphanet database⁹⁵; Germany lists 46 and Italy eight, while Sweden and Finland have none (cf. Table 2.1). As reference value, around 100 patients were known to suffer from Pompe's disease in France in 2009.⁹⁶

However, the number of diagnosed and treated persons with this disease also differs significantly from country to country. While most EU-15 MS reported steadily increasing numbers of patients every year, this is not the case in most new MS. In Romania, for example, only one patient has been diagnosed with Morbus Pompe and is treated with Myozyme, no patient has been diagnosed in EE, BG and LV until September 2010.

Altogether, using Orphanet, no expert clinic could be identified for Pompe's disease in nine countries and for PAH in 14 countries. This confirms that the process of creating, identifying and designating Centres of Expertise has not yet started or is still in very early stage in the majority of the Member States. Orphanet provides a list of centres but it is up to the national Orphanet representatives (at least one in every MS) to identify centres. The criteria for identifying and designating such clinics are applied differently in the MS. Orphanet's definition of CoE does not coincide with EUCERD's definition (see chapter 2).

The EMINET Survey results show that for Pompe's disease all 23 responding CoE from 15 Member States (of 90 addressed) monitor their patients regularly and provide long term treatment. In addition, all responding centres reported that they undertook initial diagnosis for this type of disease as well as for other Lysosomal Storage Diseases. Although nine CoE reported research activities, formalised cross-country collaboration was rarely established. Several experts explained that they occasionally exchanged professional expertise with colleagues from other countries (e.g. authors of published articles) and that they cooperated in very complex diagnostic situations.

Given the scarcity of such diseases, all efforts to strengthen cross-country cooperation, by for instance creating European Reference Networks of Centres of Expertise (cf. section 2.3), as encouraged by the European Commission, seem useful. These are however only just being established for the majority of rare diseases. The survey also showed that almost all CoE were part of (university) hospitals or affiliated to one.

Regarding one of the research objectives of the present project, the purchasing of orphan medicines by CoE, it was learned that purchasing occurs along the "normal" purchasing routes of the hospital in which the CoE is established and that the prices paid are usually those of on-patent products without treatment alternatives.

⁹⁵ www.orpha.net/consor/cgi-bin/index.php

⁹⁶ Centre Hospitalier Universitaire de Nice 2010

Even so, the majority of EU countries (24 of 27 MS) apply price control policies such as external price referencing, resulting in statutory prices allowing for add-ons for the distributors (wholesalers, pharmacies). This is also true for reimbursed medicines used in the in-patient sector in most European countries. A few countries do however not regulate prices of medicines in hospitals (DK, DE, PL, UK), therefore also not regulating prices of orphan medicines dispensed there. Any price regulation applied in hospitals and their affiliated CoE only targets the maximum hospital price, which, in practice, is hard to reduce for orphans, especially if no treatment alternatives, e.g. on ATC-4 level, are available.

Purchasing of orphan products can be undertaken by the three different ways listed below. The first two of these feature types of joint purchasing in a given country (cf. Figure 4.2 for details):

- » Procurement at a centralised level, e.g. through the Ministry of Health or a national (regional) purchasing agency
- » Procurement purchasing groups at a regional (district or county) level through e.g. hospital groups
- » Procurement directly by a hospital or its pharmacy

Many MS use all of the above mentioned ways, sometimes even in parallel: A hospital can be part of a (regional) purchasing group but will buy orphans (e.g. in the case of compassionate use) directly from a wholesaler or distributor.

The research also showed that CoE typically never purchase personally but through the usual (joint) hospital purchasing body, sometimes together with the hospital pharmacy. Being a member of a joint purchasing body strengthens the market position against monopolistic providers of orphan medicinal products and is therefore especially important for small hospitals and smaller countries. A “potential” negative effect of joint purchasing, which by definition leads to the same price for all members of the purchasing group, is that this “tendered” price may, for individual members, be higher than the price previously obtained by individual negotiations. This can cause conflicts.

Regardless of whether the procurement is done at a centralised level or initiated directly by the individual hospital, it was found that two main procurement tools are used in Europe: Tenders and negotiations, and that these may also occur in parallel. The dominant purchasing strategy in eight countries (CY, EE, IT, LV, MT, NO, SE, and UK) is tendering. In Belgium, hospitals purchase directly from manufacturers, whereby they try to negotiate a price if alternative therapeutic options are available.

Under specific circumstances (e.g. in the case of compassionate use) all MS use the way of direct purchasing by the hospital, i.e. buying straight from the manufacturer or wholesaler at quoted list prices. Sometimes direct procurement also takes place at a

centralised level, by purchasing agencies or via joint hospital purchasing groups. The latter option is the most common, e.g. in the United Kingdom.

Before installing joint purchasing processes for orphan medicines by hospitals or their affiliated CoE in more than one country it may be necessary to first establish one or two central purchasing bodies (e.g. one for public and one for private hospitals) in these countries. Establishing such purchasing bodies could be a time consuming process for the Member States as all hospitals have developed their own purchasing system. Existing purchasing processes vary to a great extent, even in the same country, depending on the type of product and disease but also on the place of use, the payer of the medicines, the owner of the hospital or CoE, the region where the hospital is located or the system's framework (social insurance vs. National Health Service). Chapter 5, which is summarised in the next section 6.3, explains the variety of the reimbursement procedures for orphan products in Europe.

Any decision to introduce joint purchasing for orphan medicines also needs to consider the fact that so far no separate purchasing strategy – other than the one for all medicines or even all medical goods needed in a hospital – exists for orphans in most MS. This is an important difference to vaccines, where joint purchasing tools have been discussed as well.⁹⁷

Due to the case study approach of the report it is not possible to give “one size fits all” answers regarding the preferred purchasing strategy for orphans in Europe. Processes which had been established successfully for many years in one hospital or CoE may not be suitable for the whole country, and the optimal way of procurement for one specific orphan medicine could be inefficient for a different one. The research findings showed that a bundling of purchases of different orphan medicines from the same provider does officially not take place, the main reason for this being the low demand for many orphan medicines, even in specialised units.

6.3 Reimbursement of orphan medicines and derogatory procedures

In most countries the predominant funding source for orphan medicines are Health Insurance Schemes or National Health Services (NHS), both at federal or regional level. In the majority of cases the same payer is in charge of orphan products and common medicines. In the Netherlands the health insurers even have to pay 100% of the cost for orphan medicines used in a hospital if they are included in a special list. In almost all

⁹⁷ Petitjean 2010

countries at least some marketed orphans are part of the national positive list or the National Health Service formulary and are thus included in the “general” reimbursement system. In several countries, however, e.g., Bulgaria, Denmark or the UK national formularies or positive lists include medicines used in hospitals as well.

In a number of countries, for instance France or Austria, the public payer of an orphan medicine depends on the place of use, meaning the payer is different for out-patient or in-patient use. In addition, several countries (e.g. Bulgaria, Poland, Portugal or Lithuania) have set up therapeutic programs financed via “earmarked” (state) budgets. For orphan products used in hospitals and in their affiliated CoE funding occurs in ways similar to those applicable to other medical goods in the given hospital. Other countries, for instance Belgium, Italy or the UK have set up specific funds for the funding of selected orphans.

The EMINET survey showed that, even if the orphan was included in the general reimbursement system of a country, patients could be faced with “hurdles” before actually obtaining the medicine. Examples include the consultation of a medical specialist for the rare disease in question or a CoE (e.g., in France, the Czech Republic or Italy) or the need to obtain prior approval of a “head physician” of the payer (social insurance fund) as in Austria or Belgium. Further control mechanisms are national registries (e.g. in Italy or Portugal) or the requirement to involve patients in a therapeutic programme (e.g. Poland, Romania).

13 of the 22 countries participating in the survey (AT, BE, CZ, DK, ES, FR, IT, LV, PL, PT, SK, SE and NO) stated that patients in their country may obtain an orphan medicine even if it is not available, i.e. reimbursed through the regular reimbursement system. Five Member States (FI, IE, MT, SK, and RO) declared that this was not possible and three MS did not reply to this question. The UK explained that all authorised orphans were principally available in the NHS if needed; therefore no derogatory procedures were in place.

The derogation mentioned most often by respondents was compassionate use of unauthorised orphan medicines. Besides compassionate use two further options of obtaining unauthorised orphans were mentioned, namely clinical trials and off-label use, one example of the latter being the use of Viagra instead of the orphan Revatio (both containing sildenafil) for the treatment of PAH. These two options were, however, not explicitly investigated among Member States in the EMINet survey

The second most common derogatory procedure involved a range of (additional) administrative requirements⁹⁸ for obtaining orphans not included in the general in- or out-patient provision system such as:

- » Prior approval from the public payer (e.g., AT, BE, DK, PL, UK)
- » Conditional prescribing, that can take various forms:
 - Prescription needs to be issued in a specialist centre or CoE for the rare disease or has to be approved by a medical specialist there (e.g., FR, IT, CZ).
 - Prescription for specific indications, especially for orphans with more than one designation such as Glivec (e.g., AT, FR) or for patients with defined diseases (e.g., EE)
 - Prescription as second- or third-line therapy (e.g., AT, HU, SE)
- » Access only for patients included in therapeutic programmes (e.g., CZ, PL, RO)

Another common policy is that (some) orphan medicines are paid from a different funding agent as shown in the examples of Belgium, Bulgaria, Italy, Latvia and Lithuania.

Treatment abroad

In principle, patients who are not able to obtain necessary non-emergency medicinal treatment in time in their home country are entitled to receive treatment in another EU/EFTA country if it is covered by their (statutory) health insurance / NHS. In practice, patients have to seek prior approval of their national payer (demonstrated via the duly authorised Form S2) before they may consult, e.g. a CoE in their neighbouring country. Otherwise they will need to pay the complete treatment out-of pocket. Despite these regulations medicinal treatment of rare diseases rarely takes place in a country other than the patient's home country. None of the countries responding to the survey could give an example of an orphan product where such a situation had occurred lately. Others, such as Romania, stated that treatment with orphan medicines was not seen as a particular situation (different from the treatment of other diseases). The interviewed experts from CoE also explained that – in the very rare case of attending a non-resident patient – they were more involved in initial diagnosis and testing than in providing the actual medicinal treatment.

Eleven responding countries (ES, FI, FR, IE, IT, MT, NO, RO, SI, SK, and UK) commented that their national pharmaceutical system did not foresee any explicit derogation regarding the treatment of their patients with orphan medicines in another country. The main reason given, e.g. by FR, IT, ES, NO or SK was that an orphan medicine not

⁹⁸ Note: Administrative requirements or "hurdles" are usually set up consciously, e.g. for safety reasons or because of intended utilisation priorities or medical practice.

included in the national reimbursement system or not available at all nationally was rather imported than having the patient receive the treatment in another country. In such a situation the same rules, e.g. individual application by the attending physician or obtaining the approval of a social insurance specialist in the case of derogatory national reimbursement, were valid. Seven of 18 replying countries (AT, BE, CZ, DK, EE, LV and PL) reported that they had explicit derogatory procedures regarding the treatment (mainly genetic testing and other diagnostic procedures) of nationals in another Member State. The specific procedures were different in all countries, but often involved the same payer as for other derogations such as compassionate use (e.g. the Belgian Special Solidarity Fund is in charge of both).

6.4 Synopsis

The limited number of patients affected (36 million in the EU) and the fragmented knowledge about these across all countries in the European Union makes rare diseases a prime example of an area where European cooperation is necessary and beneficial. It is useful to support efforts of Member States to establish Centres of Expertise for rare diseases existing in their countries and to set up a framework to endorse knowledge sharing between these CoE, for instance by further developing CoE networks (ERNs) as proposed by EUCERD and others.

It was learned that the concept of CoE is used quite heterogeneously in Europe and that criteria for the selection of a CoE need to be harmonised to create pan-European CoE: The majority of MS is just in the process of establishing or creating CoE in their countries.

Currently CoE mainly treat patients from within their country and are almost always linked to a (university) hospital. Thus the actual purchasing process of orphan medicines is very much the same as for other medical goods used in this hospital. Orphans are, because of the limited number of patients and the lack of competition due to their monopoly situation, often purchased directly from the manufacturer and not tendered. In case countries have established tools to control the prices of medicines used in hospitals, such as installing a central purchasing body or a statutory price regulation, these rules are also applied to orphan medicinal products.

Regarding out-patient use, at least 15 of 22 responding EU/EFTA countries plus Germany have included the majority of orphan products in their "general" reimbursement system. For the majority of orphans however additional administrative provisions are in place. Examples are prior approval of the payer or a defined (group of) specialist(s), specific prescribing conditions, individual application of patients, obtaining prior

approval of the prescription by a CoE or the definition of the place of use (e.g. hospital).

Besides administrative requirements, derogatory reimbursement procedures mainly concerned compassionate or off-label use of orphan medicines, whereby the payer in such cases was the same as the payer of normal in- or out-patient use. In a number of countries (IT, PL, BG, BE and others) earmarked budgets, partly in the form of a therapeutic programme were available to fund orphan medicines.

Treatment with orphan medicinal products outside a patient's country of residency is still rarely the case in Europe. Eleven EU/EFTA countries explained that they rather imported the medicine than have their patients treated abroad.

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Annex

ANNEX 1: EMINet Survey on Derogatory Reimbursement Procedures for orphan products

Orphan Medicinal Products (OMPs)

EMINet Survey on Derogatory Reimbursement Procedures for Orphan Medicinal Products.



Background:

One EMINet activity of 2010 is the mapping of existing derogatory procedures for the reimbursement of orphan medicinal products (OMP) in the MS. We want to explore the current possibility for patients to obtain reimbursement for a medicine not included in the national reimbursement list or the national pharmaceuticals benefits package (e.g. provided by the National Health Service).

Objective:

Explore ways to treat rare diseases with OMPs for which the national (public) health care system does not provide access, i.e. for OMPs that are:

- 1) neither covered by the out-patient reimbursement system nor
- 2) available in hospitals.

The survey should give an overview on how patients with rare diseases can access OMP despite the fact that they are not included in their national public pharmaceutical benefit package. It should provide answers to the question under which conditions the treatment with OMPs e.g., might be obtained in other countries.

Structure:

The following online survey contains 21 questions. Please answer all questions by either ticking the checkboxes or adding comments/examples in the prepared boxes. Feel free to browse among the pages by using the "previous" and "next" button.

Note: In case you cannot finish the questionnaire at once, the "Resume later" button allows you to come back any time you want. You will be asked to enter your name, a freely selectable password and your email address in order to login at a later date.

Please complete the survey until 21.5.2010

Contact: EMINET Project Secretariat, Ms. Claudia Hahl, Mr. Florian Bachner, Tel. +43 1 51561-161 or 288, eminet@goeg.at

Disclaimer: This survey is conducted in the framework of a service contract with the European Commission (Directorate-General for Enterprise and Industry) called EMINet (European Medicines Information Network). The main objective of EMINet is to support Pricing and Reimbursement decision- and policy-makers on the national and European level. Besides the main partner GOeG/OeBIG, EASP and LSE Health are involved in its activities.

The data produced by the EMINet project shall remain confidential and shall be exclusively for internal use by the competent national administrations.

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Orphan Medicinal Products (OMPs)

EMINet Survey on Derogatory Reimbursement Procedures for Orphan Medicinal Products.



Gesundheit Österreich
GmbH



Escuela Andaluza de Salud Pública
CONSEJERÍA DE SALUD



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Data
Please fill in this information

***1) Country**



Please fill in information

***2) Name of informant**



Please fill in information

***3) Organization**



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***4) Unit**



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***5) Function**



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***6) Phone**



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***7) Email**



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I Country Overview

***8) How does your (public) health care system usually provide access to OMPs on the market?**

Check any that apply

- ☐ Via the "normal" out-patient reimbursement system (e.g. products are included in the positive list)
- ☐ Via a "specific" out-patient reimbursement system (e.g. particular rules are applicable, such as prior approval by the payer)
- ☐ OMP are provided mainly in hospitals
- ☐ A specific (national or regional) fund covers OMP irrespective of where the treatment occurs
- ☐ Patients normally have to pay their OMP out of pocket
- ☐ Other

 Please tick the most common situation(s), multiple answers possible

***9) Please give an estimation of the availability of medicinal treatment with OMP for your patients**

Check any that apply

- ☐ Access is always granted if necessary for medicinal reasons
- ☐ Access is granted in most cases if necessary for medicinal reasons
- ☐ Access is limited due to budgetary constraints
- ☐ In most cases patients have no access to OMP required
- ☐ Other

 Please tick, multiple answers are possible

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Orphan Medicinal Products (OMPs)

EMINet Survey on Derogatory Reimbursement Procedures for Orphan Medicinal Products.



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II Access to OMP - treatment options for patients in foreign EU/EFTA countries

Imagine the case of a patient with a (ultra) rare disease in your home country for which an – expensive – Orphan Medicinal Product (e.g. Elaprase® for M. Hunter) exists, that is neither reimbursed nor accessible.

Note: Please consider the availability of the medicine in question solely in the context of clinical studies as non-availability.


***10) Are there any possibilities (e. g. derogation) for a national patient to receive this OMP in another EU/EFTA country or to obtain reimbursement for it?**

Choose one of the following answers

- ☒ Yes
☐ No

 please tick

***11) Name the national legal basis for obtaining the treatment in another EU/EFTA country (legal text and reference to the relevant provisions)**

 Please explain in detail the rules and conditions to be met in order to get the treatment. Please. mention if, for instance, an individual application is necessary by patient and / or treating doctor, if a case-by-case decision is needed by the public payer, or if your country has agreements with centres of expertise in other countries, if the transport to this country is paid for as well, etc.)

***12) Please indicate examples of rare disease areas or OMP where this has already been the case.**

 Please fill in information

***13) State who is the payer if this situation occurs**
Choose one of the following answers

- ☐ National payer (national health insurance)
☐ National payer (national health insurance)
☐ National payer (national health insurance)
☐ Other

 please tick

* Other: please specify

 Please fill in information

***14) Are the mentioned rules and conditions valid only for the treatment of rare diseases and/or OMPs?**

Choose one of the following answers

- ☐ Yes, only for OMPs
- ☐ No, there is no distinction between OMPs and other medicines
- ☒ Other

 Please choose only one option

*** Other, please specify**

 Please fill in information

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Orphan Medicinal Products (OMPs)

EMINet Survey on Derogatory Reimbursement Procedures for Orphan Medicinal Products.



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CONSEJERÍA DE SALUD



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III Access to OMP - treatment options for patients in their country of residence

Imagine the case of a patient with a (ultra) rare disease in your home country for which an – expensive – Orphan Medicinal Product (e.g. Elaprase® for M. Hunter) exists, that is neither reimbursed nor accessible.

Note: Please consider the availability of the medicine in question solely in the context of clinical studies as non-availability.

***15) Are there any possibilities (e.g. derogation) for a national patient to receive this OMP in your home country or obtaining reimbursement for it nonetheless?**

Choose one of the following answers

☒ Yes

☐ No

 please tick

***16) Name the national legal basis for obtaining the treatment in your home country (legal text and reference to the relevant provisions)**

 Please fill in information

***17) Explain in detail the rules and conditions to be met in order to get the treatment.**
Please mention if, for instance, if an individual application is necessary by the patient and / or treating doctor, or rather, if the product is imported on a case-by-case basis, etc.)

 Please fill in information

***18) Please indicate examples of rare disease areas or OMPs where this has been already the case**

 Please fill in information

***19) State who is the payer if this situation occurs**
Choose one of the following answers

☐ Usual payer of medicines (e.g. health insurance, sickness fund, National Health Service, provinces, etc)

☐ A specific fund / budget line for orphans

- ☐ Owner of hospitals
- ☐ Patient him/herself
- ☒ Other

? please tick

* Other, please specify

? Please fill in information

***20) Are the mentioned rules and conditions valid only for the treatment of rare diseases and/or OMPs?**

Choose one of the following answers

- ☐ Yes, only for OMPs
- ☐ No, there is no distinction between OMPs and other medicines
- ☒ Other

? please tick

* Other, please specify

? Please fill in information

21) Additional Comments

?

Resume later

<< Previous

Submit

[Exit and clear survey]

- ☐ Owner of hospitals
☐ Patient him/herself
☒ Other

 please tick

*** Other, please specify**

 Please fill in information


***20) Are the mentioned rules and conditions valid only for the treatment of rare diseases and/or OMPs?**

Choose one of the following answers

- ☐ Yes, only for OMPs
☐ No, there is no distinction between OMPs and other medicines
☒ Other

 please tick

*** Other, please specify**

 Please fill in information

21) Additional Comments

Source: GÖG

- » Name of Centre of Expertise?
- » Country?
- »
- » Main function of your centre?
 - My Centre of Expertise is in charge of (Please answer with Yes or No; details are welcome):
 - Research for the indication:
 - Initial diagnosis of patients:
 - Long-term treatment of patients:
 - Regular monitoring of patients:
- » Is your Centre of Expertise part of a European reference network (collaboration/sharing information with other CoE abroad)?
- »
- » Provision of orphan medicinal products needed for treatment?
- » Who pays for Tracleer/Myozyme and from which budget?
- » How does your centre purchase Tracleer? (Please answer with Yes or No; details are welcome):
 - From wholesalers?
 - Directly from company?
 - Procurement via e.g. tenders?
 - Central purchase by state or region?
 - Other (please indicate)?
 - If the orphan medicinal products is procured, by whom?
- » Patients
- » Are all patients in your country referred to your centre or are there others?
- » Can initial diagnosis be received by both national and other European citizens?
If yes, how many patients from other EU countries are diagnosed in average per year or so far (ranges are fine)?
- » Can regular treatment be received by both national and other EU citizens?
If yes, how many patients from other EU countries are treated in average per year or so far (ranges are fine)?
- » How does the development of patient numbers in your centre look like (trends)?