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Policies and availability of orphan medicines in outpatient care in 24 European countries

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ABSTRACT

Purpose: To assess pricing and reimbursement policies specific to orphan medicines and the availability and distribution settings of ten recently authorised medicinal products suitable for outpatient care with orphan status and centralised marketing authorisation in Europe, and whether patients receive these products free of charge or have to pay some or all of the costs themselves.

Methods: Web survey to authorities and representatives of third party payers in the Pharmaceutical Pricing and Reimbursement Information (PPRI) network in April 2016.

Results: In most of the 24 countries, special policies were not implemented in the assessment of reimbursement status (22 countries) or in the pricing (20 countries) of orphan medicines. An average of five of the ten recently authorised products per country were available for outpatient care. Products were dispensed from community pharmacies in eight countries and from health care units in five countries. In four countries, both distribution settings were used. When products were dispensed from community pharmacies, patients typically paid some of the price themselves. Products dispensed from health care units were often free of charge for patients.

Conclusions: Most European countries had not implemented pricing and reimbursement policies specific to orphan medicines. The availability of orphan products varied between countries. It is important to discuss whether orphan medicines should be considered as a separate group in the reimbursement regulations in order to secure patient access to these medicines.

1 INTRODUCTION

Orphan medicines are intended to treat, prevent or diagnose rare diseases [1]. Rare diseases are life-threatening or chronically debilitating diseases with low prevalence and often genetic origin. There is no universal definition for rare diseases [2]. In the European Union (EU), a rare disease is defined as a disease affecting five or fewer people in every 10,000 inhabitants. In the United States, the corresponding ratio is less than one in every 1,500 inhabitants. More than 350 million patients worldwide suffer from rare diseases and approximately 250 new rare conditions are identified annually [3-4].

Good availability of orphan medicines has been regarded as one of the priority health issues in Europe and worldwide [5]. A medicine can be considered available when it has been granted a marketing authorisation and brought to the market [6]. Accessibility presumes besides availability that the patients have no organisational, financial, or other barriers to using the medicine [7]. It has been estimated that less than one in ten patients with rare diseases receive disease-specific treatment [8]. This may be because developing orphan medicines is not always profitable for the pharmaceutical industry, as patient numbers are low and development costs high. To encourage the development and implementation of orphan medicines in Europe, the EU has offered, through the Orphan Regulation, pharmaceutical companies the opportunity to apply for orphan status for products under development [9]. Among other things, orphan status gives access to protocol assistance in the pre-marketing phase and market exclusivity once the medicine is marketed. Since the launch of the Orphan Regulation, between 2000 and 2017, the European Medicines Agency (EMA) has received 2,974 applications, of which 1,952 have been granted orphan status [10]. A total of 142 orphan medicines have received centralised marketing

authorisation. However, granting orphan status and marketing authorisation does not suffice as access to orphan medicines also depends on national pricing and reimbursement policies, which vary between countries [11]. In Europe, the cost burden of orphan medicines for patients and society is often high [12-13]. In 2014, the annual median cost of orphan medicines was estimated to be €32,242 per patient, with a wide variation from €1,251 to €407,631.

Even though the challenges facing orphan medicines have been internationally recognised, research on the availability and reimbursement policies of orphan medicines is limited [5, 11]. Publications and reports are often focused on a single country [14-17] or a limited number [11, 18-23] of countries. The latest comprehensive reports on multiple European countries, which suggest considerable variation in the availability and policies of orphan medicines between countries, were published in 2007 and 2011 [24-25]. Thus, there is a need for updated and more detailed research on this topic in Europe [5].

2 AIMS

The aim of this study was to assess the availability of orphan medicines in outpatient care in Europe. More specifically, we studied whether special policies had been implemented for assessing the reimbursement status or pricing of orphan medicines. We also studied the availability and distribution settings of ten recently authorised orphan products suitable for outpatient care, and whether patients receive these products free of charge or have to pay some or all of the costs themselves.

3 MATERIAL AND METHODS

The study was conducted as a web survey among members of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network [26]. At the time of the study, the network consisted of representatives of the competent authorities and third party payers of more than 90 institutions from 46 countries, mainly European ones. An invitation to participate and a link to the survey were sent via e-mail in April 2016.

The survey questionnaire consisted of 11 open-ended and structured questions (Appendix 1). The survey was piloted in two PPRI network organisations in Finland and minor modifications were made to the survey form based on the pilot. The survey included questions on the pricing and reimbursement policies specific to orphan medicines used in outpatient care. Furthermore, it included product-specific questions on the availability and distribution settings of ten orphan products (Table 1). It also included questions on whether patients receive these products free of charge or have to pay some or all of the costs themselves. The products included were centrally authorised medicines with a valid orphan status approved by the EMA. They were selected from the European public assessment report register of orphan designations [27] retroactively starting from the end of 2013. As the study focused on orphan medicines suitable for outpatient care, infusions and injectable medicines were excluded. The respondents were asked to give their contact information. Where additional information was needed, the respondents were contacted and requested to provide this to ensure accurate reporting.

Appendix 1

Table 1

The study setting and research process were in accordance with the local and national ethical instructions for research [28-29]. According to these instructions, this study did not require an ethical review.

4 RESULTS

After one reminder, 24 countries (52%) responded to the survey. All were European countries. Data was received from Albania, Austria, Belarus, Bulgaria, the Czech Republic, Estonia, Finland, Germany, Hungary, Iceland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Russia, Slovakia, Slovenia, Spain, Sweden, Turkey and the United Kingdom. Of these, 18 were EU member states and hence they recognise EU marketing authorisations [27]. Of the six non-EU countries, Iceland and Norway recognise EU marketing authorisations as such, and Albania as a part of the national authorisation procedure [30-32]. Belarus, Russia and Turkey do not recognise EU marketing authorisations [33-35]. Respondents were employed by the local Ministry of Health (n=10), health or social insurance institutions (n=5), medicines agencies (n=4), medicines pricing committees (n=4) or a national research institute (n=1).

4.1 Special policies on pricing and reimbursement

Most of the countries had not implemented any special regulations or policies for assessing the reimbursement status (22/24) or pricing (20/24) of reimbursable orphan medicines used in outpatient care (Table 2). Typically, the reimbursement and pricing criteria for orphan medicines were similar to those used for other medicines. Besides or apart from the special regulations or policies, other special arrangements were reported in a total of 13 countries (Table 2). In Italy, for example, marketing authorisation holders could apply for reimbursement and pricing procedures before the European Commission granted the marketing authorisation, as soon as the EMA's Committee for Medicinal Products for Human Use (CHMP) positive opinion was granted. Orphan medicines were also given priority over other reimbursement and pricing applications. In some countries, orphan medicines were funded from separate budgets. This was the case in Latvia and Russia, for example. In Latvia, the special budget programme was directed at children and was carried out by a university hospital, which procured the medicines. Cost-containment measures for expensive medicines in general were implemented for orphan medicines, too. In countries such as Finland, Hungary, Lithuania and Spain, the reimbursement of orphan medicines could be limited to defined clinical conditions, and Hungary and Russia required that the medicine was prescribed in a certain health care setting. Orphan medicines could also be subjected to price-volume agreements and confidential discounts. In Italy, on the other hand, marketing authorisation holders of orphan medicines were excluded from the payback arrangement.

Table 2

4.2 Availability and distribution setting

Twenty-three countries reported on the availability and distribution setting of the orphan products studied (Table 3). The average number of available products per country was five, ranging from zero to ten. All products were available in three countries (Malta, the Netherlands and Poland). From five to nine products were available in ten countries (Austria, Finland, Germany, Iceland, Italy, Norway, Slovakia, Spain, Sweden and the United Kingdom) and from one to four products in six countries (Bulgaria, the Czech Republic, Estonia, Hungary, Russia and Slovenia). None of the products were available in four countries (Belarus, Latvia, Lithuania and Turkey). Even if products had not been launched in some countries, they could be imported from abroad and made available for individual patients with suitable conditions. This was the case in Turkey, for example.

Table 3

Products intended for outpatient care were most commonly dispensed from community pharmacies (n=8: Austria, Finland, Germany, Hungary, Malta, Norway, Russia and Slovenia) (Table 3). In five countries (Iceland, Italy, Poland, Spain and the United Kingdom) they were dispensed from health care units such as hospitals and health care centres. In four countries (Bulgaria, the Netherlands, Slovakia and Sweden) the distribution setting varied between products.

4.3 Patients' share of the costs

Data on patients' share of the costs of the medicines was requested only when the product was available in outpatient care. Data was received from 19 countries (Table 4). In 14 countries (Austria, Bulgaria, the Czech Republic, Finland, Germany, Hungary, Iceland, Italy, the Netherlands, Norway, Slovenia, Spain, Sweden and the United Kingdom) patients in most cases either paid part of the price or received products free of charge. When products were reimbursed and dispensed from community pharmacies, patients typically paid part of the price themselves (Table 3, Table 4). Products dispensed from health care units were often free of charge for the patients. In five countries (Estonia, Malta, Poland, Russia and Slovakia) the majority of the available products were non-reimbursable (Table 4).

Table 4

5 DISCUSSION

In this study, we examined whether special policies on reimbursement status or pricing of orphan medicines used in outpatient care had been implemented in Europe. In addition, we studied the availability and distribution settings of ten recently authorised orphan products, and whether patients receive these products free of charge or have to pay some or all of the costs themselves. According to the findings, most European countries had not implemented special regulations or policies for assessing the reimbursement status or pricing of orphan medicines. Some special arrangements, e.g. separate budgets, existed however. The number of available orphan products varied between countries. Products were most commonly dispensed from community pharmacies, but dispensing from health care units was also common. When reimbursable products were dispensed from community pharmacies, patients typically paid some of the price themselves. Products dispensed from health care units were often free of charge for patients.

The number of available orphan products varied across European countries, an average of half of the products studied being available. Similar results were published by Habl & Bachner in 2011, who reported wide heterogeneity in the availability of orphan products [25]. In our study, the number of available orphan products was lower in Eastern European countries than in Central or Western European countries. It may be that countries with higher gross domestic product (GDP) can include a greater variety and more expensive medicines in their reimbursement system, while in countries with lower GDP, the availability or reimbursement of high-cost medicines may be restricted due to budgetary constraints [19, 25, 36-37]. It might also be that pharmaceutical companies do not launch their products in countries with low prices or low sales and for this reason the number of available products may be lower. However, the number of orphan products on the market is also affected by regional differences in the prevalence of rare diseases [25].

Our results show that patients generally pay some of the costs when products are dispensed from community pharmacies, and receive products free of charge when they are dispensed from health care units. Orphan and other high-cost products intended for outpatient care can be dispensed from inpatient facilities for at least two reasons. Firstly, these products may

not fit into the pricing and reimbursement schemes used in outpatient care [38], and secondly, dispensing from hospitals lowers the costs as hospital medicines are typically purchased through tendering procedures. From the patient's perspective, dispensing from hospitals may improve access to medicines in the sense that there are no out-of-pocket costs. When dispensed from pharmacies, the reimbursement status of a medicine is a basic prerequisite for patient access [11]. In order to gain a more comprehensive view on the accessibility of orphan products in outpatient care, factors such as the prices of medicines, patient out-of-pocket costs, patients' income level and other costs of health care should also be taken into account [39-40]. Regardless, if the reimbursement is high enough and a patient can afford the out-of-pocket costs, good accessibility can be fulfilled.

Assessing the value of orphan medicines for reimbursement decision can, however, be challenging as strategies used in decision-making may apply poorly to orphan medicines. For example, making a reliable cost-effectiveness analysis requires good evidence from clinical efficacy and a lot of background information. Clinical trials of orphan medicines are often non-controlled and conducted with small patient cohorts using surrogate outcome measures. Small patient populations mean there is also a shortage of information on the established management practices needed to model the evaluation. As orphan medicines are high-priced, they often fail to meet the cost-effectiveness criteria used. It has been stated that general methods for evaluating medicines are not suitable for orphan medicines as disease severity and rarity, the lack of suitable alternative treatments, and ethical principles on opportunity costs and social solidarity should also be given emphasis in the evaluations of orphan medicines [41-42].

This study has several strengths. It provides up-to-date information on the pricing and reimbursement policies of orphan medicines in up to 24 European countries. The respondents of the study were competent authorities with new and accurate knowledge of the current situation in their country. Furthermore, data was collected at the product-specific level. Data on ten recently authorised orphan products provides valuable information on the introduction, distribution and reimbursement status of orphan medicines across European countries. This study also has limitations. It does not provide precise information on the prices of medicines or patient out-of-pocket costs, which are important components of the accessibility of orphan medicines. Furthermore, medicines pricing and reimbursement schemes vary between countries [9, 18-20, 22, 24-25] and devising a universal questionnaire was challenging. Thus, it is possible that we did not obtain all adopted policies specific to orphan medicines. It should also be noted that EU marketing authorisations were not fully or partly recognised in all participating countries, and hence selected orphan products might not have been authorised. Lack of authorisation might have affected the availability of products in these countries. However, there were only four countries of this kind, and the authorities in those countries reported whether selected products were available based on the national authorisation procedure.

The number of orphan medicines and their budget impact is increasing [12, 43]. Between 2000 and 2005, the EMA granted 343 orphan designations, while in 2017 alone the corresponding number was 147 [10]. In Europe, orphan medicines' share of the total pharmaceutical market is predicted to increase from 3.3% in 2010 to 5.9% in 2020 [12]. Growing budget pressure influences not only the authorities who decide on the introduction and reimbursement of orphan medicines but also clinicians making patient-level decisions and applying patient-specific criteria, as well as affecting the patients themselves, as the policy measures adopted may give access to, or compromise, effective care [18].

Mechanisms to assess orphan medicines are just taking shape in Europe. There is a need for reports on the measures adopted and the experience gained on the policies specific to orphan medicines. Particularly, there is a need for reports

describing and characterising common themes in orphan medicine policies. There is also a need for further research on other components affecting the accessibility of orphan medicines, such as the economic burden of patients with rare diseases at both country-specific and disease-specific levels.

CONCLUSIONS

Most European countries had not implemented pricing and reimbursement policies specific to the orphan medicines used in outpatient care. The availability of ten recently authorised orphan products varied between countries. When products are dispensed from community pharmacies, patients typically pay some of the price themselves. Products dispensed from health care units are often free of charge for patients. It is important to discuss whether orphan medicines should be considered as a separate group in reimbursement regulations in order to secure patient access to these medicines.

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CONTRIBUTIONS OF AUTHORS STATEMENT

All authors have made a substantial contribution to 1) the conception or design of the work (the acquisition, analysis, or interpretation of data for the work), 2) drafting the work or revising it critically for important intellectual content, and 3) final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPLIANCE WITH ETHICAL STANDARDS

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Table 1. Orphan products selected for the product-specific section of this study

Product name	**Formulation**	**Active ingredient**	**Indication**	**EMA marketing authorisation**
Bosulif	tablets	bosutinib	chronic myeloid leukaemia	27/3/2013
Bronchitol	capsules with dry powder for inhalation	mannitol	cystic fibrosis	13/4/2013
Iclusig	tablets	ponatinib	chronic myeloid leukaemia, acute lymphoblastic leukaemia	1/7/2013
Imnovid	capsules	pomalidomide	multiple myeloma	5/8/2013
Kalydeco	tablets or granules	ivacaftor	cystic fibrosis	23/7/2012
Opsumit	tablets	macitentan	pulmonary hypertension	20/12/2013
Orphacol	capsules	cholic acid	digestive system diseases, inborn metabolism errors	12/9/2013
Procysbi	gastro-resistant capsules	mercaptamine	cystinosis	6/9/2013
Vyndaqel	capsules	tafamidis	amyloidosis	16/11/2011
Xaluprine	oral suspension	mercaptopurine	lymphoid leukaemia	9/3/2012

Table 2. Reported implementation of special regulations or policies for assessing the reimbursement status and pricing of reimbursable orphan medicines, and other arrangements on the accessibility of orphan medicines in 24 European countries in April 2016

Country	Special regulations or policies for assessing the reimbursement status	Special regulations or policies on pricing	Other special arrangements[1]
Albania	No	No	No
Austria	No	No	**Yes**
Belarus	No	No	No
Bulgaria	No	No	No
the Czech Republic	No	No	**Yes**
Estonia	No	No	No
Finland	No	No	No
Germany	No	**Yes**	**Yes**
Hungary	No	No	**Yes**
Iceland	No	No	**Yes**
Italy	No	No	**Yes**
Latvia	No	No	**Yes**
Lithuania	**Yes**	No	No
Malta	No	No	No
the Netherlands	No	No	No
Norway	No	No	No
Poland	No	No	**Yes**
Russia	**Yes**	**Yes**	No
Slovakia	No	No	**Yes**
Slovenia	No	No	**Yes**
Spain	No	**Yes**	**Yes**
Sweden	No	No	No
Turkey	No	**Yes**	**Yes**
the United Kingdom	No	No	**Yes**
Number of countries	2	4	13

Table 3. Availability in outpatient care and distribution settings of ten recently authorised orphan products in 23 European countries in April 2016

Country	Products										
	Bosulif	Bronchitol	Iclusig	Imnovid	Kalydeco	Opsumit	Orphacol	Procysbi	Vyndaqel	Xaluprine	Number of products available
Austria	○	○	○	○	○	○	•	•	○	○	8
Belarus	•	•	•	•	•	•	•	•	•	•	0
Bulgaria	□	•	•	•	•	•	•	•	○	•	2
Czech Republic	•	•	•	•	-	•	•	•	•	•	1
Estonia	-	•	•	-	•	•	•	•	•	•	2
Finland	○	•	○	○	•	○	•	○	•	○	6
Germany	○	○	○	○		○	○	○	○	○	9
Hungary	○	•	○	•	•	•	•	•	○	○	4
Iceland	□	•	•	□	□	□	•	□	•	□	6
Italy	□	•	□	□	□	•	•	•	□	•	5
Latvia	•	•	•	•	•	•	•	•	•	•	0
Lithuania	•	•	•	•	•	•	•	•	•	•	0
Malta	○	○	○	○	○	○	○	○	○	○	10
Netherlands	□	○	□	□	○	○	□	○	○	○	10
Norway	○	•	○	○	○	○	•	○	•	○	7
Poland	□	□	□	□	□	□	□	□	□	□	10
Russia	○[a]	•	•	○[a]	•	○[a]	•	•	•	•	3
Slovakia	□	•	□	□	□	○	□	□	□	□	9
Slovenia	○	•	•	○	○	•	•	•	○	•	4
Spain	-		-	□	□	□	□	•	□	•	7
Sweden	○	•	○	○	□	○	•	□	□	○	8
Turkey	•	•	•	•	•	•	•	•	•	•	0
United Kingdom	□	□	□	□	□	□	□	•	□	□	9

• The medicine is not marketed or not used in outpatient care

○ At least one strength or package size of the medicine is available in outpatient care. The medicine is dispensed from community pharmacies

□ At least one strength or package size of the medicine is available in outpatient care. The medicine is dispensed from health care units, e.g. hospitals or health care centres

- Other

[a] Available in special pharmacies

Table 4. Patients' share of the costs of ten recently authorised orphan products available for outpatient care in 19 European countries in April 2016 *

Country	Products									
	Bosulif	Bronchitol	Iclusig	Imnovid	Kalydeco	Opsumit	Orphacol	Procysbi	Vyndaqel	Xaluprine
Austria	○[a]	○[a]	○[a]	○[a]	○	○			○[a]	○[a]
Bulgaria	○								○	
Czech Republic					○					
Estonia	•			•						
Finland	□		□	•		□		•		□
Germany	□	□	□	□		□	□	□	□	□
Hungary	□		□						□	□
Iceland	○			○	○	○		○		
Italy	○		○	○	○				○	
Malta	•	•	•	•	•	•	•	•	•	•
Netherlands	○	•	○	○	○	○	○	○	○	○
Norway	□		□	□	□	□		□		□
Poland	•	•	•	•	•	○	•	•	•	•
Russia	•			•		•				
Slovakia	•		•	•	•	□	•	•	•	•
Slovenia	○			○	○				○	
Spain				○	○	○	○		○	
Sweden	□		□	□	○	□		○	○	□
United Kingdom	○[b]	○[b]	○[b]	○[b]	○[b]	○[b]	○[b]		○[b]	○[b]

* Respondents were instructed to answer only if the product was available for outpatient care in their country

• Patients pay the whole price themselves; the product is non-reimbursable

○ No out-of-pocket costs to the patient

□ Patients pay part of the price themselves

[a] No out-of-pocket costs to the patient in justified exceptional cases after prior approval by a chief medical officer

[b] No out-of-pocket costs to the patient for National Health Service (NHS) treatment. Patients pay the whole price themselves for private, non-NHS treatment