Patient Access to Medicines for Rare Diseases in European Countries

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ABSTRACT

Background: The number of authorized orphan and non-orphan medicines for rare diseases has increased in Europe. Patient access to these medicines is affected by high costs, weak efficacy/safety evidence, and societal value. European health care systems must determine whether paying for expensive treatments for only a few patients is sustainable. Objectives: This study aimed to evaluate patient access to orphan and non-orphan medicines for rare diseases in 22 European countries during 2005 to 2014. Methods: Medicines for rare diseases from the Orphanet list, authorized during 2005 to 2014, were searched for in the IMS MIDAS Quarterly Sales Data, January 2005 – December 2014 (IQVIA, Danbury, CT). The following three measures were determined for each country: number of available medicines, median time to continuous use, and medicine expenditure. A medicine was considered available if uninterrupted sales within a 1-year period were detected. Results: From 2005 to 2014, 125 medicines were authorized and 112 were found in the search. Of those, between 70 (63%) and 102 (91%) were available in Germany, the United Kingdom, Italy, France, and the Scandinavian countries. These countries were also the fastest to enable continuous use (3–9 mo). Only 27% to 38% of authorized medicines were available in Greece, Ireland, Bulgaria, Romania, and Croatia, which took 1 to 2.6 years to begin continuous use. A country's expenditure on medicines for rare diseases in 2014 ranged between €60.2 and €31.9/inhabitant. Conclusions: Patient access to medicines for rare diseases varies largely across Europe. Patients in Germany, Scandinavian countries, Switzerland, France, and the United Kingdom can access larger numbers of medicines in shorter time. Keywords: availability, medicine expenditure, orphan medicines, patient access, rare disease.

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Rare diseases are usually chronic, life threatening, or chronically debilitating and affect up to 5 in 10,000 people [1–3]. They are often poorly recognized and treated [1,4]. Although each rare disease affects only a few individuals, together they affect around 6–8% of the total European population [1,3,5]. Several regulatory and financial incentives have enhanced the research and development of new medicines for rare diseases (e.g., the European Medicines Agency [EMA] orphan designation) [1,6,7]. These incentives have increased the number of authorized medicines for rare diseases [1,8,9]. In addition to the medicines with the orphan status, other medicines for rare indications that are not designated as orphans have been authorized [2,9]. The international European portal for rare diseases, Orphanet, provides a complete list of both based on the European Commission’s Community Registers on orphan medicines and medicines suggested for orphan designation [9].

Patient access has several interpretations and is determined by several factors, including time to regulatory approval, market availability, or reimbursement; reasons for delays in these times; outcomes of technology appraisals; and conditions of reimbursement, including prescribing restrictions and copayments [9–14]. This study investigates the following three factors of patient access to medicines for rare diseases: how many medicines are available, median time to continuous use, and medicine expenditure.

The main concerns in providing patient access to these medicines are high cost and often weaker efficacy and safety evidence [8,10,15,16]. Nevertheless, they have important societal value because they improve patient quality of life and increase highly limited treatment options of a particular rare disease [16–18]. Different health technology assessment processes and decision-making policies can lead to important differences in access to these medicines among countries [11,15,19–21]. Nevertheless, each country faces the same decision—whether paying for an expensive treatment for only a few individuals is sustainable [8,10,17,20,22–26]. Therefore, orphan and non-orphan medicines for rare diseases are available in Europe.
medicines for rare diseases represent a challenge for all health care systems in Europe [17,20].

The aim of this study was to estimate patient access to different medicines for rare diseases from the comprehensive Orphanet list in various European countries in the past decade.

**Methods**

Patient access was estimated using the following three aspects: the number of medicines for rare diseases in continuous use, time to their first continuous use, and total medicine expenditure. The data analysis was performed in IBM SPSS v23.0 and Microsoft Excel. The data are presented as frequencies of available medicines and the median times to continuous use. Medicine expenditures are presented as the total annual sales (€).

**Scope of Medicines for Rare Diseases**

The study included medicines for rare diseases from the Orphanet list, authorized via centralized procedure at the EMA between 2005 and 2014 [1,10]. The Orphanet list comprises the medicines with a rare disease indication with and without the orphan designation from the EMA. Three medicines containing sitaxentan sodium, rilonacept, and dextromethorphan/quinidine were withdrawn from the European market during the inclusion period (2005–2014) and were thus excluded from the start of the study.

**Selected European Countries**

We included all the largest European countries, along with smaller ones for which the sales data from the IMS MIDAS Quarterly Sales Data, January 2005 – December 2014, were available. The following 22 European countries were analyzed: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom (UK).

**Study Period**

The medicines for rare diseases that were authorized between January 1, 2005, and December 31, 2014, were included. The sales data were obtained for the same period.

**The IMS Health Data**

Quarterly value sales from the IMS MIDAS Quarterly Sales Data, January 2005 – December 2014 (IMS Health Data; IMS Health Incorporated, Danbury, CT) were used [27]. These data were used for all medicines in the scope and for those European countries where sales data of the full medicines list could be found [27].

Each medicine from the Orphanet list was searched using the official product name at the EMA and the name of the active substance. This two-fold approach provided true information for the majority of the medicines. Some products may not have been identified because the IMS Health Data records the medicines under only one international name. In such cases, an internet search was performed to find other brand names of the product.

Despite the two-fold search, 13 products were not clearly identifiable because their product names were imprecise. Among these medicines were a tobramycin and mannitol inhalation powder; four human immunoglobulins; two filgrastim agents; and six other medicines containing everolimus, afamelanotide, lomitapide, bosentan, and a combination of human coagulation factor VIII and human von Willebrand factor. In cases of lomitapide, tobramycin inhalation powder, and one of the human immunoglobulins, similar product names were detected, but the sales data for these products appeared before the marketing authorization dates of the medicines originally searched. For the remaining 10 medicines, different product names were detected according to the search by active substance; however, these were approved for other indications (e.g., immunoglobulins were only detected according to “human immunoglobulin” showing products that could be used for several indications) or their sales data appeared before the marketing authorization date of the medicines originally searched. Therefore, we excluded these 13 products from the analysis to avoid potential bias (Tables S1 and S2 in the Supplementary Materials found at https://doi.org/10.1016/j.jval.2018.01.007).

The complete sales data for the medicines detected in the database were accessible for 22 European countries. For each country, the data were given either as hospital and retail panel separately or as hospital and retail combined. For 16 countries, both panels were given separately. In the case of Sweden, the combined data were reported. For Austria, Greece, Hungary, and Ireland, only retail sales data were available. Table S3 in the Supplementary Materials (found at https://doi.org/10.1016/j.jval.2018.01.007) presents the types of IMS Health Data reported for each country.

**Data Analysis**

First, the total number of medicines authorized between 2005 and 2014 was investigated according to the year of authorization. Main indication fields of these medicines were also searched using the Anatomical Therapeutic Chemical classification [28]. Furthermore, we investigated the following three main patient access measures for each of the 22 European countries: the number of medicines available, the median time to first continuous use after marketing authorization, and the medicine expenditure during the study period. All measures were observed for all medicines for rare diseases, together and separately, with and without the orphan status.

**Medicine Availability**

A medicine was considered available if continuous sales were detected in the database. Continuous sales were sales without interruption within a 1-year period, meaning that they were detected in four consecutive quarters (Q) (i.e., Q4-2010, Q1-2011, Q2-2011, Q3-2011). However, a 1-quarter gap (zero sales in one quarter) within the 1-year period was allowed (i.e., Q4-2010, gap, Q2-2011, Q3-2011 or Q4-2010, Q1-2011, gap, Q2-2011 or Q4-2010, Q1-2011, Q2-2011, gap). In all the presented cases, Q4-2010 was noted as the period of first continuous use. This way, one-time-only use or potentially nondistributed medicine supplies could be excluded.

The time to first continuous use was determined for each country for the available medicines. The time difference was calculated between the date of the first continuous use and the marketing authorization date. If continuous sales were detected before marketing authorization, the marketing authorization date was considered as the time of first continuous use. No negative times were considered because they could represent other means and mechanisms of patient access, such as compassionate use. The times were then compared among the countries as absolute times, and a pooled value was determined for all countries.

**Medicine Expenditure**

Medicine expenditure for each country was calculated directly from the sales at a manufacturer price reported in the IMS Health Data using constant euro exchange rate [27]. The proportions of medicine expenditure spent on medicines with and without orphan designation were also calculated. Furthermore, the sales
data were weighted by population size. The total country population data were obtained from the World Health Organization Global Health Expenditure Database [29]. Finally, a comparison was made among countries’ medicine expenditures in euros per capita, according to the country-specific total pharmaceutical sales reported in the Organisation for Economic Co-operation and Development (OECD) data portal [30]. Total pharmaceutical sales included sales for prescription medicines in pharmacies and hospitals. Some countries reported total pharmaceutical sales as sales in pharmacy only. The data for Bulgaria, Croatia, and hospitals. Some countries reported total pharmaceutical sales included sales for prescription medicines in pharmacies and Development (OECD) data portal [30]. Total pharmaceutical sales reported in the Organisation for Economic Co-operation and Development (OECD) data portal [30].

**Results**

**Number of Medicines Authorized in Europe**

Between 2005 and 2014, 125 medicines for rare diseases were approved. Among them, 71 were granted the orphan designation by the EMA. The other 54 medicines are used for different rare diseases but do not have the orphan designation [9]. Each year, 7 to 18 new medicines for rare diseases were approved (Fig. 1). According to the Anatomical Therapeutic Chemical classification, 44% of the authorized medicines were new antineoplastic and immunomodulating medicines intended to treat rare cancers, inborn immune deficiencies, and other immune diseases (Fig. 1).

Among 125 authorized medicines for rare diseases, 13 medicines were excluded because they could not be properly identified. Finally, 112 medicines were used in the further analysis.

**Medicine Availability**

**Number of available medicines**

Of the 112 medicines included, the largest number of medicines for rare diseases were in continuous use in Germany and the UK, where 102 (91%) and 95 (85%) medicines were used, respectively (Fig. 2).

The countries continuously using between 60% and 70% of the included medicines for rare diseases were Sweden, Italy, Norway, and France. In Finland, Spain, Austria (retail data only), Slovakia, and Belgium, between 50% and 60% of these medicines are used. Among the countries, orphan medicines represent between 47% and 63% of the medicines for rare diseases in continuous use. The smallest European markets for rare diseases, according to the number of available medicines, were Greece (retail data only), Ireland (retail data only), Bulgaria, Romania, and Croatia.

Eleven medicines were available in all 22 countries included in the study. Excluding Austria, Greece, Hungary, and Ireland, which report only retail data, four additional medicines were revealed. Table 1 presents the list of medicines that were in continuous use in all the countries, according to their active substance and indication for which these were authorized.

**Time to first continuous use**

Germany had the shortest median time to first continuous use, which was 3 months after marketing authorization for both orphan and non-orphan medicines. The UK, Sweden, Norway, and Switzerland had median times of 6 months. In Austria, Finland, France, and Greece, half the medicines for rare diseases were available within 1 year after marketing authorization. Other countries were slower in enabling first continuous use, taking from 1 to 2.6 years for introducing half of the medicines available on their markets (Fig. 3).

In smaller European markets (e.g., Bulgarian, Croatian, Czech, Romanian, Slovenian), longer median times to first continuous use were observed. The times of particular available medicines in these countries were very different and took up to 5 or more years. The pooled median time value for all the countries was 1 year. Also, separate pooled median times for orphan and non-orphan medicines were both equal (1 year). The average (standard deviation) for all countries of mean times between marketing authorization and first continuous use of the available medicines for rare diseases was estimated at 1.6 (0.6) years. The average (standard deviation) of orphan and non-orphan medicines were similar, 1.6 (0.7) and 1.5 (0.6) years, respectively.

For the 11 medicines available in all countries, the pooled median time to first continuous use was 0.5 year. The individual country median times of these 11 medicines were either the same as or shorter than the times of all available medicines with the exception of Bulgaria, Croatia, and Romania, where median times were longer.

**Medicine Expenditure**

The expenses for medicines for rare diseases increased each year when new medicines were approved across all countries, except for Greece, where the expenditure decreased after 2011. The largest pharmaceutical expenditures per inhabitant for medicines for rare diseases were observed in Germany, Switzerland, France, and Belgium throughout the study period. In 2014, the expenditure for the medicines available amounted to €31.9/inhabitant in Germany and €27.0/inhabitant in Switzerland. Greece had the lowest expenditure for medicines for rare diseases, €6.6/inhabitant in 2014.
diseases in 2014, which was €0.2/inhabitant for medicines in retail sales only (Fig. 4).

The total expenditures for medicines for rare diseases were allocated differently for orphan and non-orphan medicines among the countries. The proportion of resources spent on orphan medicines in 2014 represented between 33% (Czech Republic and Poland) and 63% (Ireland) of the total expenditure on medicines for rare diseases.

Fig. 5 presents the country comparison in total expenditure for medicines for rare diseases, according to the total pharmaceutical sales reported by the OECD. The countries that seemingly allocated more money for medicines for rare diseases are Germany and Slovenia (approximately 8% of the total retail pharmaceutical sales). Norway and Czech Republic allocated fewer resources for these medicines (approximately 3% of the total pharmaceutical expenditure in hospitals and pharmacies) compared with other European countries. Also, the expenses for medicines for rare diseases in Austria, Ireland, and Hungary were lower than in other countries, but only retail sales data are presented for these countries.

Discussion

This study provides an insight to patient access to medicines for rare diseases in 22 European countries. Previous published studies assessed patient access and budget impact of orphan-designated medicines only, whereas the scope of this study is broader [14,22,23,25,31,32]. Herein, all medicines authorized in Europe to treat rare diseases are included, irrespective of the
orphan medicine status [1]. Some countries (e.g., Bulgaria, Croatia, Romania, and Slovenia) representing smaller European pharmaceutical markets that have not been studied before are also included.

Our results confirm that the number of medicines for rare diseases has increased since after 2010 and that the number of medicines in use and the resources spent vary widely among European countries [31,32]. Despite these differences, some medicines are available in all countries and are mostly indicated for treating rare cancers and immune diseases. Similarly, the European Organisation for Rare Diseases (EURORDIS) study in 2010 showed that oncology medicines for rare diseases were the most widely available in nine European countries analyzed [33]. Furthermore, our mean time to first continuous use seems to be comparable with the findings from the 2007 EURORDIS study that included 17 European countries [32]. The study reports the mean European time to first use of orphan medicines as 341 days (0.93 y) after marketing authorization [32]. In our study, the average time to first continuous use assessed for orphan medicines was 1.6 years, which seems longer, but it represents uninterrupted use and includes the times of slower European markets. We demonstrated that times to first use for orphan and non-orphan medicines did not differ in the biggest markets, whereas some smaller markets needed more time to introduce orphan medicines compared with non-orphan medicines, which could be due to higher prices [34,35]. Our overall results show that in Europe, half of the medicines for rare diseases introduced (orphan or not) are in use within 1 year after marketing authorization. The most successful countries in providing numerous medicines to the market in the quickest time are Germany, Norway, Finland, Sweden, and France, as observed previously [31,32,36]. These countries also have specific mechanisms to improve patient access to these medicines and to grant full or substantial reimbursement from public resources [15,31,32,36]. Italy and Spain have introduced several medicines for rare diseases, but it takes them longer than 1 year until the medicines are first used. In addition, Italy enables full reimbursement of orphan medicines, whereas Spain covers medicines with therapeutic advantage [15,21].

Austria and The Netherlands also provide many medicines in a short time and substantially cover orphan drugs [15,21,37].

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**Fig. 3** – Median plot with times to first continuous use of medicines for rare diseases for each European country. The countries are listed according to the increasing median times for orphan and non-orphan medicines, respectively. Upper and lower bars represent the values of third and first quartiles, respectively. Time differences are given as point estimates of quarterly data. The median times for all medicines for rare diseases available in each country are given in parentheses. M, median; M_pooled, pooled median value; m – months.

**Fig. 4** – Total expenditure for orphan and non-orphan medicines for rare diseases in 2014, presented in euros per inhabitant for each country. *Only retail sales data were available.*
some of the smallest markets, such as Slovenia, also seem to
have high proportional costs compared to the total medicines’
expenditure, which could be because here the OECD data do not
include hospital consumption, as they do for other countries, and
therefore expenditure for rare diseases seems to account for a
greater proportion of the total sales. Norway and Czech Republic
differ from other countries in the study in that they spend less on
medicines for rare diseases; yet, lower medicine prices in both
countries need to be considered [37].

The leading country in all the aspects studied was Germany,
as confirmed in the 2007 EURORDIS study, where many medi-
cines were available (91%) at the fastest time (median time of 3
mo) and the most resources per inhabitant were spent on
medicines for rare diseases (£31.9/inhabitant) [32]. On the other
hand, Germany’s prices were among the highest in Europe,
probably due to the free pricing system and the fact that it is
widely used as a reference country by other countries
[15,23,34,36]. Nevertheless, Germany seems to be a good example
of fast patient access to the majority of medicines for rare
diseases [15,23,40].

The Scandinavian countries (Finland, Norway, and Sweden)
and the UK also were among the most successful in terms of
availability [15,31,32]. Even though their total pharmaceutical
sales per inhabitant were as much as or even greater than those
in Germany, their expenditures for medicines for rare diseases
per inhabitant were much less than those in Germany. Never-
theless, the prices of medicines in the Scandinavian countries are
much lower [21,37]. In addition, in Sweden and Norway, orphan
medicines are mostly fully reimbursed, whereas this varies in
Finland from 65% to 100% [15,21,36,37,41].

Similarly, the UK enables many medicines in short time but
has even lower medicine expenditure than do the Scandinavian
countries, which could be due to fixed pricing within the Phar-
maceutical Price Regulation Scheme [15,23,36]. However, in the
UK, reimbursement is approved only if cost-effectiveness criteria
are met or if the National Cancer Drug Fund covers the treatment
[15,21,36].

Nevertheless, the comparison of patient access among the
countries based on the IMS Health Data might not reflect the
actual situation across Europe. The IMS Health Data are limited in
terms of quality and type of data reported by different countries
and therefore provide only patient access estimation.

In addition, expenditure for medicines for rare diseases could
in some cases overestimate the true cost because some medi-
cines are also used for other indications. On the other hand,
taking the 13 products that were unidentifiable in the IMS Health
Data according to their product names or active substance into
account could have resulted in greater overall medicines
expenses, especially due to medicines with human immunoglo-
bulins, for which four of five medicines that were approved in the
study period had to be excluded for that reason. Still, the data-
base is useful in showing a minimal available collection of
medicines for rare diseases in use, and it serves for calculation
of time to their access. Continuous use implies that the medicine
is probably effectively in use and distributed to patients. Never-
theless, the time when continuous use begins does not necessa-
ri ly mean that the medicine is reimbursed at that point because
the national decision-making bodies can take several months to
decide on reimbursement, even for top-selling medicines [13,40].

Finally, the number of patients requiring the treatment might
vary from country to country depending on disease prevalence
and potential prescribing restrictions. The 2010 EURORDIS study
assessed the approximate proportion of patients with actual
access to the orphan medicines at 63% to 73% of all the orphan
medicines launched [33]. In this study, total country populations
were used to compare different countries because the true
region-specific prevalence and incidence of rare diseases were

Fig. 5 – Total annual country expenditure on medicines for
rare diseases in 2014 (in euros per inhabitant) according to the
total pharmaceutical sales in 2014 reported by the
Organisation for Economic Co-operation and Development.
Total pharmaceutical sales data were not reported in the
Organisation for Economic Co-operation and Development
database for Bulgaria, Croatia, Greece, Poland, and Romania,
which therefore are not presented. *Only retail sales data
were available. Black diamonds, retail and hospital
consumption included in the total pharmaceutical sales; grey
diamonds, only retail consumption included in the total
pharmaceutical sales.

Similarly, Ireland is fast in enabling first use, but reimbursement
depends on community and national schemes that may not
cover the medicine [15]. Also, the number of medicines reported
is quite low and does not represent total product availability.

Smaller markets, such as the Bulgarian, Croatian, Czech,
Greek, Hungarian, Polish, Romanian, Slovenian, and Slovakian
markets, offer between one-third and one-half of the medicines
analyzed, which is a significant number of medicines for rare
diseases. However, the time to first use is much longer and more
variable in these markets than in the larger European markets.
Possible reasons for the fewer number of medicines are weaker
sales reporting to the IMS Health Data and decisions of pharma-
cutical companies when to launch the product [34]. Smaller
markets usually refer to larger ones with higher prices in external
reference pricing, so fewer medicines and longer delays can be
expected [34,37]. Nevertheless, some of these, such as Bulgaria,
Croatia, Czech Republic, Hungary, Romania, Poland, Slovakia, and
Slovenia, have a special reimbursement regimen that covers the
total costs for most orphan medicines [14,15,31,38,39]. In contrast,
in Greece, medicines are reimbursed if they are cost-effecti ve
and patients must provide a copay when the reference price is
exceeded [15,39].

The largest expenditures on medicines for rare diseases were
observed in the countries with greatest numbers and fastest use,
such as Germany, Switzerland, France, and Belgium. The most
numerous products also were available in these markets [32]. All
these countries have substantial reimbursement; Germany has
full coverage, Belgium has a Special Solidarity Fund for rare
diseases, France offers at least partial reimbursement, and
Switzerland reimburses with a 10% copayment limited with an
annual threshold [14,15,21]. The prices of medicines for rare
diseases in these countries were as much as or more expensive
than those in other countries [14]. When accounting for the total
pharmaceutical sales, the proportion spent on medicines for rare
diseases per inhabitant seemed to be the greatest in some of the
same countries: Germany, France, and Switzerland [23]. However,
largely unknown [2,16,42]. The results of our study should be interpreted in the context of real-life patient needs. That said, the best indicator of accessibility to a medicine would be to measure the proportion of patients who are actually receiving medicines that are reimbursed [10,43].

**Conclusions**

Important differences in the availability and expenditure for medicines for rare diseases exist among European countries. Patients in Germany, the Scandinavian countries, Switzerland, France, and the UK can access larger numbers of medicines in shorter time than in other European countries. The three countries with the largest expenditures on medicines for rare diseases were Germany, Switzerland, and France.

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**Supplementary Materials**

Supplemental material accompanying this article can be found in the online version as a hyperlink https://doi.org/10.1016/j.jval.2018.01.007 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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