AN INSIGHT ON DIFFERENCES IN AVAILABILITY AND REIMBURSEMENT OF ORPHAN MEDICINES AMONG SERBIA, BULGARIA AND SWEDEN

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ABSTRACT

In the European Union (EU), rare diseases are defined as life-threatening or chronically debilitating diseases with prevalence lower than five in 10,000 inhabitants. Although individually rare, together, rare diseases affect a significant part of the population (27–36 million people in the EU). Therefore, patient access to orphan medicines is receiving increasing political attention in the EU.

In order to assess the differences in availability of reimbursed orphan medicines among Serbia, Bulgaria and Sweden, National Reimbursement Lists were reviewed and identified orphan medicines were crossed with the List of orphan drugs in Europe, published in July 2011, available from Orphanet. The analysis of regulatory traits was based mainly on a review of the official documents setting out legislation regarding rare diseases and orphan medicines in the studied countries.

Only 6.5 % (4 out of 61) of the authorised orphan medicines in Europe with prior orphan designation and 25.0 % (17 out of 68) without prior orphan designation were available and reimbursed in Serbia. In the Bulgarian Positive Drug List 44.3 % (27 out of 61) of the drugs with prior orphan designation and 50.0 % (34 out of 68) without prior orphan designation were identified. The share of reimbursed orphan medicines was the highest in Sweden among the observed countries – 52.5 % (32 out of 61) of the medicines with orphan designation and 60.3 % (41 out of 61) without prior orphan designation. According to the first level of the ATC Classification System, most of the reimbursed orphan medicines in the three studied countries belonged to the group L: “Antineoplastic and immunomodulating agents”, while the most common indications for authorised and reimbursed orphan medicines were “Neoplasms” (C00-D48), with 19 available orphan drugs in Serbia, 26 in Sweden and 31 in Bulgaria.

Inequities in the access to orphan medicines among Serbia, Bulgaria and Sweden may be explained by the differences in the approaches for registration, pricing and reimbursement of orphan medicines. The low share of reimbursed orphan drugs in Serbia may be due to incomplete compliance with EU legislation and existence of domestic procedure for authorisation as well. The EU legislation and policy on treatment of rare diseases obviously facilitate the penetration of orphan drugs on the EU market, but apparently there is also considerable budget impact on the availability of reimbursed orphan medicines.

Keywords: orphan medicines, rare diseases, legislation, reimbursement, health policy, comparative analysis

Introduction

In the European Union (EU), rare diseases are defined as life-threatening or chronically debilitating diseases with a prevalence lower than five in 10,000 inhabitants (17). Orphan drugs are medicines used in the diagnosis, prevention and treatment of rare diseases or medicinal products that would not be developed without incentives because their sales are unlikely to generate sufficient return on investment (25). It is accepted that currently there exist 5,000–7,000 rare diseases, with approximately 250 new diseases being described annually (30). Since the majority of the rare diseases (80 %) have identified genetic origin, many of them are inborn or appear in childhood, mainly errors of metabolism. Other rare diseases are a result of bacterial or viral infections and allergies, or are due to degenerative or proliferative causes. Although individually rare, together, rare diseases affect significant part of the population. They are estimated to be about 6 % to 8 % of the population of the European Union (EU), equivalent to 27–36 million people (12). Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities (19). Regulation (EC) No 141/2000 on orphan medicinal products states that “patients suffering from rare conditions should be entitled to the same quality of treatment as other patients” (17).

The orphan drug designation, allowed by the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA), is based on three criteria: epidemiological data/insufficient return on investment, medical plausibility and potential benefit (31). The present system of orphan designation allows for drugs for non-orphan diseases to be designated as orphan drugs (5). By the end of December 2010, more than 850 positive opinions for orphan medicinal product designation have been adopted from 1,235 applications that have been reviewed since April 2010 by
the COMP (31). Until July 2011, 61 medicinal products with orphan designation have received marketing authorisation in the EU. This comprises gene therapy medicinal products, somatic cell therapy medicinal products, and tissue-engineered medicinal products (20). Considering estimates that currently 5,000-7,000 rare diseases are described, it is obvious that the vast majority of these conditions do not yet have a specific drug treatment.

Orphan drug designation and marketing authorisation are EU centralised procedures. Meanwhile, decisions governing pricing and reimbursement of orphan drugs are a Member State responsibility. As a result, evidence requirements, pricing and reimbursement policies governing orphan drugs differ between countries (25). Therefore, access to medication for rare diseases is very heterogenous among the Member States of the EU, as reported in surveys by Alcimed in 2005 and Eurodis in 2004 and 2007 (8). National drug reimbursement committees are facing the trend of the increasing number of new orphan drugs entering the market and expect a relative increase in the budget spent on orphan drugs as compared to drugs for more common diseases mainly because of the high prices charged for these orphan drugs (15). However, the countries of South-East Europe are republics in transition (although some of them are already Member States of the EU) and it is difficult for local governments to allocate money on rare disease treatment (26).

Therefore, the aim of our study was to evaluate differences in access to orphan medicines among two South-East European countries – Serbia (a part of former Yugoslavia and currently a candidate for EU membership), Bulgaria (EU Member State since 2007), and the Scandinavian country Sweden, chosen for its highly developed social and healthcare system.

Materials and Methods

In order to identify potential differences between orphan drug availability and reimbursement in selected countries, a comparative study was performed. The information about authorised orphan medicines in Europe was obtained from the List of Orphan Drugs in Europe published in July 2011, available from Orphanet (11), which is expert-authored and peer-reviewed database of rare diseases available on the Internet (www.orpha.net). The list includes drugs with orphan designation that have also been granted European market authorisation under the centralised procedure. The list also includes medicines without orphan designation as long as they have been granted a marketing authorisation with a specific indication for a rare disease. The data on the level of orphan medicine availability and reimbursement in the observed countries were retrieved from the databases of the representative national authorities containing National Reimbursement Lists. We reviewed the Positive Drug Lists (PDL) of Serbia and Bulgaria (13, 18), while the information about orphan drugs registered and reimbursed in Sweden were collected from the Dental and Pharmaceutical Benefits Agency (TLV) medical products database (6). Orphan drugs availability in these countries was analyzed by crossing medicines identified in the Reimbursement Lists with those in the List of Orphan Drugs in Europe.

The analysis of the regulatory traits of rare disease and orphan drug markets in the studied countries was based on a review of the international literature and the official documents setting out legislation regarding rare diseases and orphan medicinal products.

Results and Discussion

Orphan medicines legislation in studied countries

Serbia

It is estimated that there are approximately 500,000 patients suffering from rare diseases in Serbia (14). Although a National Register for rare diseases does not exist in Serbia, the Law on Healthcare (supplements to the Law as of 2011) (23) provides for the forming of the official centres of reference for rare diseases that have the obligation of diagnosing, treatment and patient counseling, but also of the creation of a National Register.

Neither policy measures, nor research incentives for rare diseases exist in Serbia. Given that Serbia is not a EU Member State, it does not have representatives in the European Committee for Orphan Medicinal Products (COMP), but the National Organisation for Rare Diseases of Serbia (NORBS) is a part of the European Organisation for Rare Diseases (EURORDIS) that has its representatives in the COMP (14).

Orphan drugs are authorised through the EMA centralised procedure, but there is also a domestic procedure for marketing authorisation in Serbia. For the medicines that have already been registered via the centralised procedure, domestic procedure for authorisation is expedited, according to the Law on Medicines and Medical Devices (24). In the same Law, it is also stated that there are no fees for authorisation of orphan drugs and that orphan drugs may be conditionally registered until the marketing authorisation holder (MAH) has met all obligations.

Serbia, as a country with a low gross domestic product (GDP), disposes only 300 Euro per capita for funding the total healthcare system (out of which 50 Euro go for drug funding), which is less than in neighbouring countries. When assessing a reimbursement application, the Central Expert Committee for Medicines (CSK) of the Republic Fund of Health Insurance (RFZO) takes into account the cost-effectiveness of the drug, budget impact, but also the need for a given treatment (18). Orphan drugs in Serbia are reimbursed by RFZO, funded through the payment of health insurance contributions. Additionally, a special fund has been created to reimburse medical expenses for rare diseases that are not reimbursed by the Health Insurance Fund. This Fund is provided by the Health Insurance Act (22) and by the Games of chance Act (21) as of 2011 in which it is stated that one part of the budget revenue of the Republic from game winnings taxes will be used for funding the treatment of rare diseases.
Bulgaria
The Council Recommendation from 2009 on an action in the field of rare diseases recommends that EU Member States establish and implement plans or strategies for rare diseases in order to ensure that patients with rare diseases have access to high quality care, including effective orphan drugs if possible (4). Bulgaria has adopted the National Plan for rare diseases and the implementation is now under way. One of the main priorities of the Plan is creating a national register of rare diseases (3).

An Information Centre for Rare Diseases and Orphan Drugs (ICRDOOD) is established in Bulgaria. There are also different patient groups organised under the Bulgarian National Alliance of People with Rare Diseases (NAPRD) (28). The national legislation on orphan medicines comprises the Health Law (1) and the Law on Medicinal Products in Human Medicine (2), which introduces the definitions of rare diseases and orphan medicines and regulates the access to treatment. There are six disease management centres for diagnosis and treatment of rare diseases, dedicated to approximately 400,000–450,000 patients in Bulgaria (27).

The orphan medicines are registered through the centralised procedure, but in order to make them affordable on a national level, a price needs to be registered and a procedure for funding needs to be regulated. Both processes are controlled by the Ministry of Health in Bulgaria. The Law on Medicinal Products in Human Medicine (2) refers to Regulation (EC) 141/2000 and sets up the conditions for marketing authorisation of orphan medicines, their pricing and funding. It is stated there that orphan drugs are the part of the Positive Drug List, which means that orphan medicines are funded either by the Health Insurance Fund or by the state budget for the diseases which are excluded from the scope of the obligatory health insurance (27).

Sweden
The National Board of Health and Welfare (Socialstyrelsen), as a government agency under the Ministry of Health and Social Affairs, founded the Swedish Information Centre for Rare Diseases that acts as a national resource of information on rare diseases. In Sweden, the official definition of rare diseases is “disorders resulting in substantial disability and affecting no more than one hundred individuals per million population”. In spite of this narrow definition, rare diseases affect about 100,000 persons in Sweden, according to an estimation (29).

In compliance with Regulation (EC) 726/2004, orphan drugs in Sweden are authorised via a centralised procedure only. Although Article 9 of Regulation (EC) 141/2000 calls for national incentives to be made by the EU Member States, neither policy measures nor research incentives for rare diseases and orphan drugs exist (5). There are specialised centres for rare diseases on a regional level in Sweden and there are also several rare disease support groups organised in a national alliance – Rare Diseases Sweden (16).

Reimbursement decisions are taken by the Dental and Pharmaceutical Benefits Board (DPBB), a governmental agency that determines whether a pharmaceutical product should be subsidised by the State. Reimbursement is done by the Public Social Insurance. The reimbursement procedure considers cost-effectiveness, but also the human value principle, the need and solidarity principle, which means that a higher cost-effectiveness threshold may be considered for rare diseases and orphan drugs. To gain reimbursement, the budget impact of orphan medicines is not taken into account in Sweden (15).

The level of reimbursement is the same for all types of medicines and depends on the accumulated total cost of prescribed drugs over 12 months. If the accumulated total cost of prescribed medicines has exceeded 4300 SEK (Swedish krona) the patient will receive the medicines free of charge, while if that amount is below 4300 SEK the patient will pay a part of the costs. Generally, orphan drugs are fully reimbursed by Social Insurance (16). There is free pricing of orphan drugs in Sweden through a system of public procurement at the regional level, used in order to maximise price competition (5).

Cross-country comparison
According to the List of Orphan Drugs in Europe (11), by July 2011, 61 medicinal products with prior orphan designation received market authorisation, as well as 68 medicines without prior orphan designation. Compared with the same list, only 4 orphan medicines with European market authorisation and prior orphan designation were included in the Serbian Reimbursement List, representing 6.5 % of the orphan drugs granted an orphan designation in the EU. Concerning the orphan medicines with European market authorisation and without prior orphan designation, 17 orphan drugs were identified in the Serbian Reimbursement List, representing 25.0 % orphan medicines without prior orphan designation in Europe. Taken together, 16.3 % of all authorised orphan medicines in the EU were available and reimbursed on the market in Serbia (Fig. 1).

In comparison with the Serbian market, the presence of orphan medicines in Bulgaria was more favorable. In the Bulgarian Positive Drug List 27 i.e. 44.3 % orphan medicines with European market authorisation and with prior orphan designation were identified. Also, 34 (50.0 %) authorised orphan medicines without prior orphan designation were available on the Bulgarian market and were reimbursed by the Health Insurance Fund or by the state budget. Thus, 47.3 % of the orphan medicines were found to be available and funded in Bulgaria (Fig. 1).

In Sweden 32 (52.5 %) authorised drugs with prior orphan designation were subsidised by the Public Social Insurance, and 41 (60.3 %) drugs without prior orphan designation. Therefore, 56.6 % of all orphan drugs were available and reimbursed on the Swedish market (Fig. 1). The share of authorised and reimbursed orphan medicines, both with and without prior orphan designation, was the lowest in Serbia and
the highest in Sweden, while that share in Bulgaria had a closer value to that in Sweden.

Based on the first level of the Anatomical Therapeutic Chemical (ATC) Classification System, orphan drugs (both with and without prior orphan designation) reimbursed in Serbia relate to 5 therapeutic groups, including: ‘L – Antineoplastic and immunomodulating agents’ (14 drugs), ‘J – Antiinfectives for systemic use’ (3 drugs), ‘G – Genitourinary system and sex hormones’ (2 drugs), ‘B – Blood and blood forming organs’ (1 drug) and ‘N – Nervous system’ (1 drug). According to the same classification system, reimbursed orphan medicines in Bulgaria belong to 9 therapeutic groups, mainly ‘L’ (32 medicines), ‘A – Alimentary tract and metabolism’ (8 medicines) and ‘B’ (6 medicines). Similarly, in Sweden, reimbursed orphan drugs include 9 therapeutic groups, mainly ‘L’ (29 drugs), ‘A’ (12 drugs) and ‘B’ (10 drugs). Group ‘A’ was found to be the second most frequent group for reimbursed orphan drugs in Sweden and Bulgaria, while there were no reimbursed orphan medicines belonging to group ‘A’ in Serbia (Fig. 2 and Fig. 3).

![Fig. 2. Number of reimbursed orphan medicines with prior orphan designation by ATC code.]

Using the International Classification of Diseases (ICD), which is the standard diagnostic tool for epidemiology, health management and clinical purposes, we analysed what rare diseases can be treated with reimbursed orphan medicines in Serbia, Bulgaria and Sweden. The results showed that the most common indications for all three countries are ‘Neoplasms’ (C00-D48), with 19 available orphan drugs in Serbia, 26 in Sweden and 31 in Bulgaria. The second most frequent ICD category is ‘Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism’ (D50-D89), with only 2 reimbursed orphan drugs for these indications in Serbia, 11 in Bulgaria and 18 in Sweden. Similarly, there are 2 reimbursed orphan drugs for ‘Endocrine, nutritional and metabolic diseases’ (E00-E90), 12 in Bulgaria and 15 in Sweden. The other common indications for
reimbursed orphan medicines in the studied countries include ‘Diseases of the nervous system’ (G00-G99), ‘Diseases of the musculoskeletal system and connective tissue’ (M00-M99), and ‘Certain conditions originating in the perinatal period’ (P00-P96), with no reimbursed medicines available for the last mentioned ICD category in Serbia (Fig. 4). Our analysis demonstrated that amongst the studied countries, the patients in Sweden have better access to orphan drugs, followed by Bulgaria and Serbia. The inequities in the access to orphan medicines among Serbia, Bulgaria and Sweden may be explained by the differences in the approaches for registration, pricing and reimbursement of orphan medicines. The low share of orphan drugs with European market authorisation that are available and reimbursed in Serbia may be due to incomplete compliance with the EU legislation (although the Serbian healthcare system has changed considerably since 2000) and existence of domestic procedure for authorisation as well, which leads to delay in access to orphan drugs.

The EU legislation and policy on treatment of rare diseases obviously facilitate the penetration of orphan drugs on the EU market. However, although Bulgaria and Sweden are both EU Member States, still there are a lot of orphan medicines that are not reimbursed there; 34 medicines with prior orphan designation and 34 medicines without prior orphan designation are not reimbursed in Bulgaria and 29 medicines and 27 medicines, respectively, are not reimbursed in Sweden. Apparently, the budget issues affect the availability of reimbursed orphan medicines in different countries. Amounts of gross domestic product (GDP) based on purchasing power parity (PPP) per capita for Serbia (10,642 international dollars), Bulgaria (13,597 international dollars) and Sweden (40,394 international dollars) in 2011 (10) may partly explain differences in the level of reimbursement among the studied countries.

Conclusions
The results of our study suggest that the Serbian health legislation should be further complied with important European regulations governing rare diseases and orphan medicines in order to improve the access to orphan medicines and thus, the treatment of patients with rare diseases in Serbia. Likewise, our results are in agreement with the proposal, recently developed by Eurordis, industry and academic leaders in the field of orphan medicines, for a more harmonised European pricing and reimbursement process which would probably prevent inequities in access to orphan medicines among EU Member States (7, 8).

Despite the relatively low number of patients with rare diseases, treatment with orphan medicinal products has a significant impact on the health care budget, especially with an increase in the number of new orphan medicines in future. In order to efficiently control the public pharmaceutical spending, countries need to constantly change and improve their policies.

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