

A CROSS-COUNTRY COMPARISON OF REIMBURSED ORPHAN MEDICINES IN BULGARIA, GREECE AND ROMANIA

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ABSTRACT

Rare diseases are orphan diseases with low prevalence, affecting not more than 5 per 10 000 Europeans. Despite the common European Union (EU) political framework in the field of rare diseases and orphan drugs (ODs), there are differences in patient access to orphan drugs in different EU member states.

The aim of this study was to evaluate the access to ODs and to compare it in light of the reimbursement systems in three neighboring Balkan EU Member States: Bulgaria, Greece and Romania. The policy and legislation documents related to rare diseases and ODs were reviewed and a cross-comparison between the Orphan Drug List in the EU for a six-month period (May 2012–October 2012) and the reimbursement drug lists available in each of the studied countries was made.

The available and accessible ODs with European authorization and prior orphan designation (of a total of 68 ODs) in October 2012 were 24 (35.3 %) in Bulgaria, 45 (66.18 %) in Greece, and 36 (52.94 %) in Romania. The biggest ATC group in the studied countries was that of the 'L - Antineoplastic and immunomodulating agents'. No 'R-Respiratory system' medicines were found in the reimbursement lists. The dynamics in the reimbursement of available ODs with European authorization and with prior orphan designation within the six-month period showed the most remarkable increase in Romania (27.94 %). The number of ODs with European authorization and without prior orphan designation (of a total of 75 ODs) included in the Bulgarian Reimbursement List were 40 (55.33 %); in Greece, 52 (69.5 %); and in Romania, 44 (58.66 %). The ATC group 'L - Antineoplastic and immunomodulating agents' was again the largest. There were no 'C - Cardiovascular system' and 'P - Antiparasitic products' ODs. The most notable dynamics in the reimbursement of available ODs with European authorization without prior orphan designation were observed in Greece (a 38.08 % increase).

This is the first study comparing and analyzing the dynamics in OD access in the neighboring countries Bulgaria, Greece and Romania. It showed that although there are regulatory frameworks in the field of rare diseases in the three countries, the access to ODs is different, it being lower in Bulgaria. As it was expected, neither one of the countries reimburses all EU authorized for sale orphan drugs with and without prior orphan status designation.

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Introduction

Rare diseases are diseases with a particularly low prevalence. The European Union (EU) considers diseases to be rare when they affect not more than 5 per 10 000 persons in the EU (23). It is believed that between 5 000 and 8 000 distinct rare diseases exist, affecting between 6 % and 8 % of the population, equivalent to a total number of 27–36 million people affected by rare diseases in the EU (14).

Most rare diseases are genetic diseases and the rest include rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases etc. Due to their low individual prevalence, rare diseases in general have traditionally been neglected by large parts of the scientific, medical and political communities but latest scientific developments, especially in the genetic field, are creating increasing awareness because a lot of rare diseases have become manageable (24).

Since the 1990s, at both an EU and Member State (MS) level, political concepts and initiatives concerning rare diseases have emerged. In the 1990s, some of the MSs led the way to the first European legislative text concerning rare diseases, the Orphan Medicinal Product Regulation of 16 December 1999, and the ensuing Commission Communication (2008) and Council Recommendation (2009) (9). Sweden and Denmark first established centers of expertise for rare diseases; in Italy, a decree on rare diseases came into force in 2001; and in France, Orphanet was established in 1997, followed by the first national plan/strategy for rare diseases in Europe (2004). A number of other countries, amongst which are Bulgaria and Greece, elaborated national plans for rare diseases at the very same time as the EU policy in the field was defined through the Commission Communication and Council Recommendation (10).

The political framework for action in the field of rare diseases and orphan medicinal products at European level is established by three key policy documents: The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products) (23); The Commission

Communication on Rare Diseases: Europe's challenge, adopted on 11 November 2008 (6), and The Council Recommendation on an action in the field of rare diseases adopted on 8 June 2009 (7). To aid the European Commission with the preparation and implementation of Community activities in the field of rare diseases, the European Union Committee of Experts on Rare Diseases (EUCERD) was formally established via the European Commission Decision of 30 November 2009 (2009/872/EC) (5). The European Commission has also funded The European Project for Rare Diseases National Plans Development (EUROPLAN), a three-year project which began in 2008 with the main goal to provide national health authorities with supporting tools for the development and implementation of national plans and strategies for rare diseases as recommended by the Council (10). These documents not only create the European legislative framework, but also are the prerequisite for the creation of national legislative basis.

The availability and affordability of orphan drugs, medicinal products developed for treatment of rare diseases, is a significant part of the public health policies in EU MSs. Orphan drug designation and marketing authorisation of orphan medicinal products are EU centralised procedures. The orphan drug designation, allowed by the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA), is based on the following criteria: epidemiological data/insufficient return on investment, medical plausibility and potential benefit (29). The present system of orphan designation allows for drugs for non-orphan diseases to be designated as orphan drugs and, thus, to increase the availability of medicines for rare diseases at the European level (8). By October 2012, 68 medicinal products with prior orphan designation had received marketing authorisation in the EU. They comprise gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered medicinal products (17).

Unlike these procedures, the decisions governing the pricing and reimbursement of orphan drugs are MS responsibility and, as a result, the pricing and reimbursement policies differ in different countries (26). The number of newly marketing authorised orphan drugs is constantly increasing and their inclusion into the national reimbursement schemes is a heavy burden on the budgets dedicated to medicinal products, especially for countries most suffering from economic crises (1).

The aim of our study was to make a cross-country comparison of the access to orphan medicines through reimbursement systems in three neighboring Balkan EU Member States: Bulgaria, Greece and Romania.

Materials and Methods

Policy and legislation analysis

Internet search was done to identify the related policy and legislation documents regarding rare diseases and orphan drugs in the studied countries. The documents found were analyzed with respect to the historical development, main stakeholders,

rare diseases covered, and process of reimbursement approval. The regulatory publications were reviewed and analyzed from the perspective of their role for ensuring access to adequate pharmacotherapy.

Cross-country comparison

In order to study any potential differences between orphan drug availability and reimbursement in the selected countries, we performed a comparative study of the orphan drugs included in the reimbursement drug lists.

First, we obtained information about the authorized orphan medicines in Europe from the List of orphan drugs in EU for a six-month period (May 2012–October 2012) (17), including orphan medicines with and without prior orphan designation.

Then, we searched the officially published reimbursement drug lists of the three countries. Information on the orphan medicine availability in these countries was systematized by INN and ATC code from the databases of the representative national authorities for National Reimbursement Lists (18, 19, 20). The availability of orphan drugs was analyzed by crossing orphan medicines identified in the National Reimbursement Lists with those in the List of Orphan Drugs in Europe, as well as among the three countries.

Results and Discussion

Rare diseases and orphan drug policy and legislation documents

Table 1 presents the main policy and legislation indicators reflecting the access to orphan drugs in the analysed countries.

Bulgaria. In 2008 Bulgaria adopted a National Plan for Rare Diseases with several priorities set towards creation of a national register for rare diseases; prevention of genetic rare diseases by enlarging the current screening programmes; introducing new genetic tests, decentralisation of the laboratory activities and easier access to medico-genetic counselling; introduction of integrative approach to the prevention, diagnostics, treatment and social integration of patients with rare diseases; promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases; organisation of a national information campaign; collaboration with non-governmental organizations and patient associations for rare diseases as well as with other EU MSs. The document stated that there are 400 000–450 000 patients with rare diseases in the country (4).

The Bulgarian national legislation on orphan medicines is defined by the Health Law (2) and Law on Medicinal Products in Human Medicine (3), which introduces the definitions of rare diseases and orphan medicines and regulates the access to treatment.

The approval of medicine prices and reimbursement status are controlled by the Ministry of Health. The Law on Medicinal Products in Human Medicine refers to Regulation (EC) 141/2000 (23) and sets up the conditions for marketing authorisation of orphan medicines, their pricing and

TABLE 1

Policy and legislation indicators in the selected countries

	Bulgaria	Greece	Romania
Population (mln)	7.46	11.304	21.390
Patients with rare disease (n)	400 000–450 000	1 000 000	1 300 000
Prevalence (%)	5.5–6	8.8	6–8
National Register	Yes	No	Yes
National policy document	Yes	Yes	Yes
Legislation documents	Health law and Law for medicines, National strategy for rare diseases	Law for medicines	Law for medicines
Reimbursement documents	Separated list of the PDL, funded by the NHIF or Ministry of health	Approval by the Greek National Organization for Medicines or Institute of Pharmaceutical Research and Technology	National program for rare diseases

TABLE 2

Dynamics of availability of reimbursed orphan drugs with prior orphan designation

	According to the May 2012 List (number of medicines)	According to the October 2012 List (number of medicines)	Increase in availability (%)
EU	54	68	-
Greece	24	45	28.68
Romania	16	36	27.94
Bulgaria	22	24	0.91

TABLE 3

Dynamics of availability of reimbursed orphan drugs without prior orphan designation

	According to the May 2012 List (number of medicines)	According to the October 2012 List (number of medicines)	Increase in availability (%)
EU	64	75	-
Greece	20	52	38.08
Romania	22	44	24.29
Bulgaria	37	40	-4.48

reimbursement. Orphan medicines are funded either by the National Health Insurance Fund, or by the state budget for the diseases which are excluded from the scope of the obligatory health insurance. Since 2011, EUCERD has noted a tendency to gradually transfer the treatment coverage of all rare diseases from the Ministry of Health to the National Health Insurance Fund. However, the Ministry of Health remains a major player in rare disease treatment provision with the Fund for Children's Treatment and Commission for Treatment Abroad (11).

In 2003, the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) was established as a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES) with the aim to provide free

educational and information services including personalized replies to requests from patients, families and medical professionals in the field of rare diseases and orphan medicinal products. In 2010 ICRDOD started publishing reviews on rare diseases.

There are around 30 rare disease patient groups organized under the umbrella of the Bulgarian National Alliance of People with Rare Diseases (NAPRD) (28). On 28 October 2009, BAPES (Bulgarian Association for the Promotion of Education and Science) was officially given the status of data privacy administrator of rare diseases registries by the Commission for Protection of Data Privacy. Following the very successful model of the national registry of thalassaemia

major patients, BAPES has recently initiated five new rare disease registries (11).

Bulgaria also contributes to the EUROCARE CF and TREAT-NMD European registries. Several national best practice guidelines are available in Bulgaria, for example the guidelines prepared, adopted and published by the Bulgarian Cancer Society for oncological diseases, including rare tumours, clinical guidelines for Gaucher disease, thalassemia, neuromuscular diseases, etc. (11).

Greece. In Greece there are approximately 1 000 000 people suffering from rare diseases (15). One year before the adoption of the Bulgarian National Plan for Rare Diseases (2009–2013), the Greek National Plan for Rare Diseases (2008–2012) was prepared by a commission composed of government officials, health professionals and patient representatives and approved by the Greek Minister of Health (20). Two years later, in 2010, the provisions of the Greek National Plan were discussed during the Greek National Conference on Rare Diseases co-organised by the Greek Alliance for Rare Diseases (PESPA) and EURORDIS and held in Athens (26–27 November 2010) in the framework of the Europlan project (12). The need to establish universal access to orphan drugs was identified as one of the priorities during the conference. According to the 2012 EUCERD Report on the State of the Art of the Rare Disease Activities in Greece (12), none of the strategic priorities points in the Greek National Plan have yet started probably due to the lack of both legal frameworks for the plan and allocated budget. During the past decades, units providing expert services for groups of a limited number of diseases including some rare diseases have been organized within the Greek health system. The Hellenic Centre for Disease Control and Prevention (KEELPNO) collects data on activities of these units and aims to complete the collection in 2012. By the end of 2011, there were 15 centers of expertise for thalassemia, six centers for neuromuscular diseases, four centers for hereditary bleeding disorders, three centers for cystic fibrosis and two centers for primary immunodeficiency. Currently, there is no national registry for rare diseases in Greece.

In 2003, leading health professionals and presidents of 20 rare disease national and regional patient associations established PESPA (the Greek Alliance for Rare Diseases). Numerous national patient organizations exist in Greece mainly for the more prevalent rare diseases such as thalassemia, hemophilia, cystic fibrosis etc.

The Greek National Organisation for Medicines (EOF) ensures the public health and safety of all medicinal products, including orphan medicinal products (21). Orphan medicinal products that are not available on the Greek market are imported by the Greek Institute of Pharmaceutical Research and Technology, and transferred to the patients requiring these drugs.

Romania. Approximately 6 % to 8 % of the Romanian population (1 300 000 people) suffers from rare diseases and around 1 250 000 of these patients do not yet have a correct or complete diagnosis, nor treatment or adequate care (25).

In 2008, the Romanian Ministry of Health and the country's National Alliance for Rare Diseases (RONARD) signed an accord to form a partnership ("Rare Diseases, a priority for health care in Romania") in order to instate a national plan for rare diseases, following work which started in 2007 (13). Later, the country's 2008 health budget was readjusted to include funding for various elements of the rare disease plan and the "national program for haemophilia, thalassaemia and other rare diseases" came into force in June 2008. In August 2009, a National Committee for Rare Diseases was composed with the main aim to elaborate the Romanian National Plan for Rare Diseases. In July 2011, the Romanian Association for Rare Cancers was established and later in November, rare cancers were included in the proposal for the National Plan for Rare Diseases. In 2011, the Ministry of Health Rare Diseases Operative Commission was founded, coordinated by the National Committee for Rare Diseases. It is directly involved in elaborating and executing the decisions of the National Committee for Rare Diseases. A Rare Disease Commission has also been created at the University of Medicine and Pharmacy in collaboration with the Member States Rare Diseases Commission.

In 2011 the budget allocation for the National Program for Rare Diseases was increased by €2 000 000: 43 more patients affected by rare diseases were included in the program (seven patients with Hunter syndrome, three patients with Harley syndrome, a patient with congenital afibrinogenemia and 33 patients with congenital primary immunodeficiency).

Currently there are no official centers of expertise in rare diseases in Romania, and the genetic diagnosis of rare diseases is carried out in medical genetics centers based in university hospitals (13). There are a number of patients' national registries in Romania for rare diseases such as hemophilia, primary immunodeficiency, infant diabetes mellitus, thalassemia, cystic fibrosis, pulmonary hypertension, hyperparathyroidism, acromegaly, neuromuscular diseases, etc.

Cross-country comparison

According to the List of Orphan Drugs in Europe (17), by October 2012, 68 medicinal products with prior orphan designation, as well as 75 medicines without prior orphan designation had received market authorization.

Availability of orphan medicines with European authorization and with prior orphan designation in the reimbursement lists. Compared with the same list in October 2012, only 24 orphan medicines with European market authorization and prior orphan designation were included in the Bulgarian Reimbursement List, representing 35.3 % of orphan drugs included in the relevant EU list. In the Greek Reimbursement List, 45 orphan drugs were identified, representing 66.18 % of the orphan medicines with prior orphan designation in Europe. Romania has reimbursed 36 (52.94 %) such drugs (**Fig. 1**).

Using the first level of the Anatomical Therapeutic Chemical (ATC) Classification System, the orphan drugs

with prior orphan designation reimbursed in Bulgaria related to seven therapeutic groups, including: 'L – Antineoplastic and immunomodulating agents' (12 medicinal products), 'A – Alimentary tract and metabolism' (five medicines), 'B – Blood and blood forming organs' (two medicines), 'C' – Cardiovascular system (two medicines) and one product from each of the following groups: 'G – Genitourinary system and sex hormones', 'Systemic hormonal preparations, excluding sex hormones and insulin' and 'V – various' (**Fig. 2**). In Greece and Romania, like in Bulgaria, the reimbursed medicines belong to the same ATC categories. The largest one is the 'L' ATC group, represented by 21 reimbursed medicines in Greece and 15 medicines in Romania, followed by 'A' (eight medicines in Greece and seven in Romania), and 'B' (three medicines in each), 'C' (three medicines in each). No 'R – Respiratory system' medicines were found in the reimbursement lists of the studied countries.

In comparison with the Bulgarian market, the presence of orphan medicines with European marketing authorization and prior orphan designation in Romania was similar, while in Greece it was far more favorable (**Fig. 1**). At the time of our study, the Greek Positive Drug List included 45 % of the orphan medicines with European market authorization and with prior orphan designation, while in the Romanian List this percentage was 26 %. Twenty-one out of 29 'L' medicinal products (72.41 %) were reimbursed in Greece, while their shares in the Bulgarian and Romanian Positive Drug Lists were 41.37 % and 51.72 % respectively.

As the List of Orphan Drugs in Europe is regularly updated, we compared the dynamics in the reimbursement availability of medicines with European marketing authorization and prior orphan designation in the studied countries within a six-month period (**Table 2**). We found just a 0.91 % increase in the number of medicines with European marketing authorization and prior orphan designation for Bulgarian patients, while Greece remarkably increased the presence of orphan drugs with prior designation in the Positive Drug List with 28.68 % (from 37.50 % to 66.18 %); and Romania, with 27.94 % (from 25 % to 52.94 %), respectively. The biggest increase in both countries was for the 'L – Antineoplastic and immunomodulating agents' group. No changes were observed in the number of reimbursed orphan medicines in the category of 'G – Genitourinary system and sex hormones', 'H – Systemic hormonal preparations, excluding sex hormones and insulins', 'J – Anti-infectives for systemic use', 'L – Antineoplastic and immunomodulating agents', 'N – Nervous system', 'R – Respiratory system' and 'V – various' in the Positive Drug List in Bulgaria. Only two orphan medicines were added: one from the 'B' and one from the 'C' group, respectively, for immune (idiopathic) thrombocytopenic purpura (ITP) and ambrisentan, in the Bulgarian Positive Drug List in comparison with the previous edition of the List of Orphan Drugs in Europe.

Availability of orphan medicines with European authorization and without prior orphan designation in the reimbursement lists. Compared with the EU List of medicines

with European authorization and without prior orphan designation, 40 orphan medicines with European market authorization and prior orphan designation were included in the Bulgarian Reimbursement List, representing 55.33 % of the relevant medicines. Fifty-two orphan drugs were identified in the Greek Reimbursement List, representing 69.33 % of the orphan medicines without prior orphan designation in Europe. Romania was found to have included 44 orphan drugs with European market authorization and with prior orphan designation (58.66 %) (**Fig. 1**).

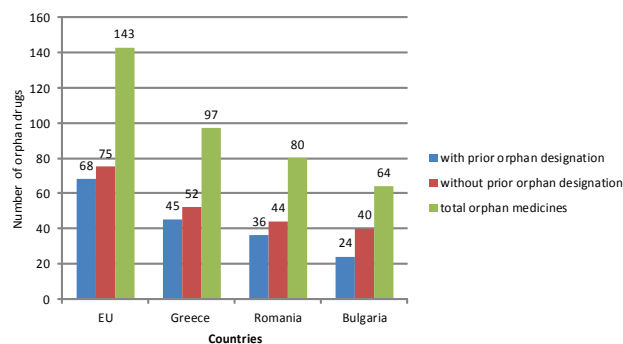


Fig. 1. Number of reimbursed orphan medicines in the studied countries: orphan medicines with European market authorisation with and without prior orphan designation in Europe.

The orphan drugs without prior orphan designation reimbursed in Bulgaria related to eight therapeutic groups including: 'L – Antineoplastic and immune modulating agents' (22 medicinal products), 'B – Blood and blood forming organs' (six medicinal products), 'J – Anti-infectives for systemic use' (three medicines), two medicinal products from each of the following groups: 'A – Alimentary tract and metabolism', 'G – Genitourinary system and sex hormones', 'H – Systemic hormonal preparations, excluding sex hormones and insulin' and 'V – various' (**Fig. 3**) and an 'N – Nervous system' medicine. In Greece, we identified medicines from nine therapeutic groups included in the Positive list, one 'R – Respiratory system' medicine being included. The reimbursed orphan medicines in Romania also belonged to nine therapeutic groups, slightly different from the Greek list, mainly 'L' (26 medicines), 'B' (four medicines), 'J' (three medicines), 'A' (two medicines), 'G' (two medicines) and 'H' (two medicines).

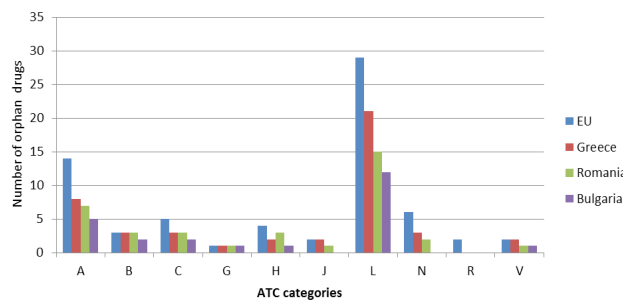


Fig. 2. Number of reimbursed orphan medicines with prior orphan designation by ATC code.

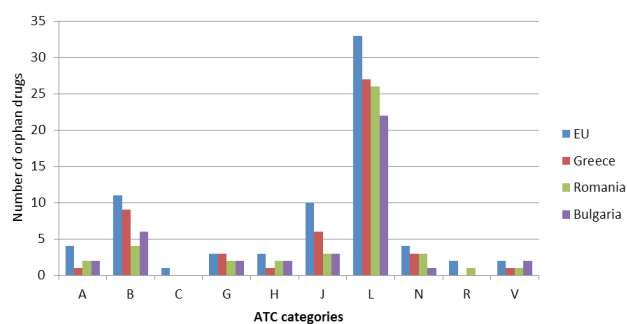


Fig. 3. Number of reimbursed orphan medicines without prior orphan designation by ATC code.

The 'L' group was the largest therapeutic group in the three countries. The 'B' group was the second most frequent group (Fig. 3). In neither of the three studied countries, were there medicines from the groups of 'C – Cardiovascular system' and 'P – Antiparasitic products'.

The analysis of the availability of medicines with European marketing authorization and without prior orphan designation in the studied countries within the six-month period (Table 3), revealed the highest dynamics in Greece with an increase of 38.08 % (from 31.25 % to 69.33 %), followed by Romania with a 24.29 % increase (from 34.38 % to 58.67 %). Bulgaria, on the other hand, decreased the availability with regards to orphan drugs with European marketing authorization and without prior orphan designation with 4.48 %.

The biggest increase in Greece and Romania was recorded in the 'L' group, followed by 'B' and 'G' group ODs. In Romania, all therapeutic groups were updated with new orphan medicines, while in Greece only the 'A' group remained unchanged. In Bulgaria only three medicines were included during the studied period: two medicines from the 'B' group (conestat alfa and human protein C) and a medicine from the 'H' group (somatropin).

Final remarks

Several authors studied the access of Bulgarian patients to orphan medicines (16, 22, 27). Some of them compared Bulgaria with other countries such as Serbia and Sweden, other analyzed the access to particular orphan medicines for a given period of time.

This work for the first time compares Bulgaria with its neighboring countries Greece and Romania, and analyses the access dynamics. It adds new evidences regarding the access to orphan medicines in countries with similar macroeconomics and morbidity patterns for a longer period. It is obvious that this is a very dynamic area and the level of ensured access changes, but whether it is in line with the national plans and healthcare system priorities remains unclear. Our analysis showed that Greece, despite of cost constraint measures, set ensuring adequate access to orphan drugs as one of the priorities of its healthcare system, while in Bulgaria the access was restricted significantly during the observed six months.

National medical care services for the diagnosis, treatment and rehabilitation of rare disease patients differ with regards to availability and quality of services. All three studied countries adopted national plans for rare diseases, aiming to develop an institutional frame and services for the diagnosis and treatment of rare diseases, to improve access to the information in the area of rare diseases and to orphan medicines and to stimulate the research as well as the role of patient organizations. However, the studied countries experience some difficulties in the implementation of national plans and ensuring adequate access to orphan medicines. One possible reason is the lack of financial framework of the national plans which made the access and affordability questionable. The other possible reason is the lack of consistency in orphan drugs evaluation for the reimbursement purposes. Some studies show that the cost-effectiveness of orphan drugs is far above the accepted threshold and Scotland even developed an ultra-orphan category. Further studies are necessary to evaluate not only the access from the point of view of presence within the reimbursement lists, but also from the viewpoint of financial affordability.

Our analysis demonstrated that amongst the studied countries, the patients in Greece have a high number of orphan drugs reimbursed, followed by Romania and Bulgaria.

The observed inequities in the access to orphan medicines among the studied countries may be explained by the differences in the approaches towards pricing and reimbursement of orphan medicines, purchasing power parity as well as budget constraints. The big difference in availability between Bulgaria and Romania could also be due to the unique project "Norwegian–Romanian (NoRo) Partnership for Progress in Rare Diseases" (2009–2011), with financial support from the Norwegian Cooperation Program for sustainable economic development in Romania.

Conclusions

The results from our study showed that the three analyzed countries (Bulgaria, Greece and Romania) have national policy documents and a regulatory basis ensuring access to orphan medicines. The access to orphan medicines through their reimbursement systems differs and it is lowest in Bulgaria. Neither one of the countries reimburses all EU authorized for sale orphan drugs with or without orphan status designation.

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