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REIMBURSED ORPHAN MEDICINES IN BULGARIA AND THE SHARE OF BIOTECHNOLOGY-DERIVED PRODUCTS

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ABSTRACT

Rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in the European Union. Most of the people suffering from rare diseases are actually affected by less frequently occurring diseases affecting one in 100,000 people or fewer. Almost 80% of the rare diseases have identified genetic origins and lots of them are treated with biotechnology-derived medicinal products. The aim of our study was to evaluate the access to orphan medicines in Bulgaria based on the analysis of the Positive Drug List (PDL) and the share of biotechnology-derived products reimbursed for rare diseases in Bulgaria. Only 21 out of 56 medicines with European orphan designation and European marketing authorisation are available and funded in Bulgaria. 29% of them are biotechnology-derived. Another 17 (out of 47) orphan medicines with European marketing authorisation and without prior orphan designations in the EU are reimbursed and 59% of them are biotechnology-derived. Thus approximately just 37% of the orphan medicines (both with and without prior orphan designation) are available and funded in Bulgaria. Evidently the centralised marketing authorisation is not supported by the national regulatory requirements for price setting and inclusion into the PDL, which are necessary for guaranteeing medicines availability on the national market. The regulators and payers still do not ensure balance between the needs of patients and resources allocation.

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Introduction

Rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in the European Union. Most of the people suffering from rare diseases are actually affected by less frequently occurring diseases affecting one in 100,000 people or fewer (5, 8, 20).

The medicines intended for treatment of rare diseases are called "orphans" because the pharmaceutical industry has little interest, under normal market condition, in developing and marketing products intended for only a small number of patients suffering from very rare conditions (1, 2, 3, 4, 5, 9, 11). Almost 80% of the rare diseases have identified genetic origins and a lot of them are treated with biotechnology-derived medicinal products.

Some conditions occur so infrequently that the cost of developing and bringing a medicinal product to the market, as well as the cost to society is questionable (6, 7). At the same time patients suffering from rare diseases should be entitled to the same quality of treatment as other patients and their medicines should be both available and affordable in the country, especially in the poor ones (8, 9).

Regulation (EC) No 141/2000 and Commission Regulation (EC) No 847/2000 provide the legislative frame for orphan medicines and rare diseases setting up the Community procedure for designation of orphan drugs and incentives to the sponsors on a Community level (10, 11). Rare diseases are presented as one of the priorities in the current European Union Public Health Program running till 2013 and in addition to the initiatives on the EU level, the member-states develop further regional programmes to ensure adequate access to pharmacotherapy (12, 14, 15, 17, 18, 19).

The Commission recommends that Member States put in place strategies organized around national plans for rare diseases and orphan medicines, adequate mechanisms for definition, codification and inventory of rare diseases and production of good practice guidelines, fostering research on rare diseases, including cross-border cooperation, ensuring access to high-quality healthcare, in particular through identifying national and regional centres of expertise (5, 18, 22). Some researches are pointing that there are differences in patients' access to orphan medicines in member state countries due to variety of reasons and their clarification is necessary in achieving the regulation goals (13, 21, 23, 24, 26).

The aim of our study was to evaluate the access to orphan medicines in Bulgaria based on the analysis of the Positive Drug List (PDL) and the share of biotechnology-derived products reimbursed for rare diseases in Bulgaria.

Materials and Methods

A regulatory analysis of the main European and corresponding Bulgarian laws and health regulations related to rare

TABLE 1

Bulgarian legislation concerning rare diseases/orphan drugs

Law/regulation/other	Scope of the document	Relation to rare diseases/orphan drugs
Health Act (6)	Public health care	• **Chapter 4 "Health protection of specific groups of the population", section 2 "Reproductive health", paragraph 127 (2), p. 5** requires prenatal diagnostics and prevention of genetic diseases. • **Chapter 4 "Health protection of specific groups of the population", section 4 "Genetic health and genetic tests", paragraph 137-144** requires treatment, prevention and diagnostics of genetic diseases, treatment of hereditary diseases
Law on Medicinal Products in Human Medicine (7)	Marketing authorisation of medicinal products, licensing of pharmaceutical manufacturers, wholesalers, retailers, clinical trials, advertising, classification, pharmacovigillance, state control over the market, pricing of medicinal products and reimbursement.	• **Chapter 3 "Marketing authorisation", paragraph 25 (1):** reference to Regulation (EC) 141/2000 regarding the criteria for orphan drug and **paragraph 25 (2)** which is reference to Regulation 762/2004 with regard to marketing authorisation of orphan drugs. • **Chapter 3 "Marketing authorisation", paragraph 27**, regarding the proof of orphan drug designation required as submission documentation for marketing authorisation. • **Chapter 12 "Pricing of medicinal products", paragraph 262, (4), p.4**: orphan drugs are part of the "positive" list (the reimbursement list). • Definition of orphan drug is given.
Ministry of Health Regulation No 34 as of 25.11.2005 (23)	Lays down the provisions for prescribing, dispatching the products for treatment of diseases which are excluded from the obligatory health insurance.	According to Regulation 34/2005, article 2, (1), p.4 the treatment of rare diseases is funded by the Ministry of Health. Obsolete as of 01.01.2007.
Ministry of Health Regulation on Positive Drug List (24)	Lays down the provisions for inclusion of medicinal products into the Positive List.	Regulates the inclusion of drugs into the positive list, including the drugs for the treatment of rare diseases.

diseases and orphan medicines was performed (27-33). The regulatory publications were reviewed and analysed from the perspective of their role for ensuring an access to adequate pharmacotherapy.

We have applied a three-step methodology in order to assess the availability of orphan drugs in Bulgaria: **(1)** Review of the List of orphan medicines in Europe (with European market authorisation and with or without prior orphan designation in Europe) for orphan medicines clarification (16); **(2)** Review of Bulgarian PDL and identification of orphan drugs included (19); **(3)** Crossing the medicines identified in **step (2)** with the List of orphan medicines in Europe (with European market authorisation and with or without prior orphan designation in Europe) to evaluate the level of orphan drug availability in Bulgaria. The methods of manufacturing for each reimbursed orphan medicine were checked in the Summary of Product Characteristics and European public assessment reports (33).

Results and Discussion

Bulgarian legislation on orphan drugs and rare diseases

Patients suffering from rare diseases in Bulgaria are estimated to be 400 000-450 000 people (5). There are six disease management centres for diagnosis and treatment of rare diseases in Bulgaria. The national legislation on orphan drugs comprises of several laws and regulations as presented in **Table 1**, each having its role for the establishment of the legislation frame of treatment of rare diseases in Bulgaria.

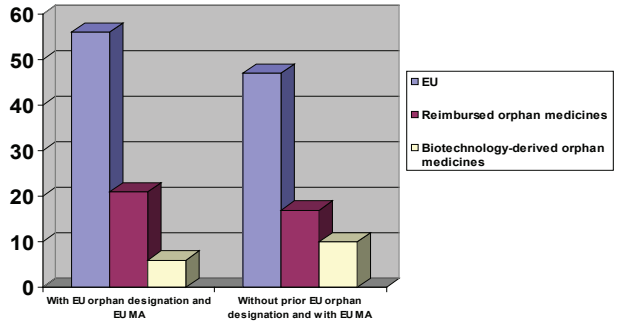

Fig. 1. Reimbursed orphan medicines and share of biotechnology-derived products

The Health Act (3) outlines the genetic examinations and prenatal tests which are aimed at limiting the incidence of rare diseases in the country. The Law on Medicinal Products in Human Medicine (4) refers to Regulation (EC) 141/2000

TABLE 2

Reimbursed orphan medicines in Bulgaria (with European marketing authorisation and prior orphan designation in Europe)

Reimbursed orphan drug/ Marketing Authorisation Holder	INN	ATC code	Manufacturing methods	Disease name
ANNEX 3				
Afinitor (Certican) /Novartis Europharm Ltd.	Everolimus	L04AA18	synthesised from commercially available starting materials	Advanced renal cell carcinoma, progressed on or after treatment with VEGF-targeted therapy
Litak/Lipomed GmbH	Cladribine	L01BB03	synthesised from commercially available starting materials	Hairy cell leukaemia
Atriance/Glaxo Group Ltd.	Nelarabine	L01BB07	synthesised from commercially available starting materials	T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic leukaemia
Exjade/Novartis Europharm Ltd.	Deferesirox	V03AC03	synthesised from commercially available starting materials	Beta-thalassaemia major
Glivec/Novartis Europharm Ltd.	Imatinib mesilate	L01XE01	synthesised from commercially available starting materials	Chronic myeloid leukaemia, gastrointestinal stromal tumors etc.
Nexavar/Bayer HealthCare AG	Sorafenib tosylate	L01XE05	synthesised from commercially available starting materials	Advanced renal cell carcinoma, hepatocellular carcinoma
Sprycel/ BMS Pharma EEIG, UK	Dasatinib	L01XE06	synthesised from commercially available starting materials	Chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia
Sutent/Phizer Ltd., UK	Sunitinib	L01XE04	synthesised from commercially available starting materials	Renal cell carcinoma, gastrointestinal stromal tumor
Tasigna/Novartis Europharm Ltd.,UK	Nilotinib	L01XE08	synthesised from commercially available starting materials	Chronic myelogenous leukaemia
Torisel/WyethEuropa Ltd.	Temsirolimus	L01XE09	synthesised from commercially available starting materials	Renal cell carcinoma, mantle cell lymphoma
ANNEX 4				
Aldurazyme/Genzyme Europe B.V.*	Laronidase	L16AB05	recombinant DNA technology (rDNA)	Mucopolysaccharidosis type 1 (MPS 1) (Alpha-L-iduronidase deficiency)
Elaprase/Shire Human Genetic Therapies AB*	Idursulfase	A16AB09	recombinant DNA technology (rDNA)	Mucopolysaccharidosis type 2 (MPS 2) (Hunter syndrome Iduronate 2-sulfatase deficiency)
Exjade/Novartis Europharm Ltd.	Deferesirox	V03AC03	synthesised from commercially available starting materials	Beta-thalassaemia major
Fabrazyme/Genzyme Europe Ltd.*	Agalsidase	A16AB04	recombinant DNA technology (rDNA)	Fabry disease
Glivec/Novartis Europharm Ltd.	Imatinib mesilate		synthesised from commercially available starting materials	Chronic myeloid leukaemia, gastrointestinal stromal tumours etc.
Myozyme/ Genzyme Europe Ltd.*	Alglucosidase alfa	A16AB07	recombinant DNA technology (rDNA)	Glycogen storage disease type 2 (Pompe disease)
Naglazyme/Bio Marin Europe Ltd.*	Galsulfase	A16AB08	recombinant DNA technology (rDNA)	Mucopolysaccharidosis type 4 (Arylsulfatase B deficiency, Maroteaux-Lamy syndrome, N-acetylgalactosamine 4-sulfatase deficiency)
Revatio/Pfizer Ltd.	Sildenafil	G04BE03	synthesised from commercially available starting materials	Pulmonary arterial hypertension
Somavert/Pfizer Ltd.*	Pegvisomant	H01AX01	recombinant DNA technology (rDNA)	Acromegaly, Acromegaly - cutis verticis gyrata - corneal leukoma
Tasigna/Novartis Europharm Ltd. UK	Nilotinib	L01XE08	synthesised from commercially available starting materials	Chronic myelogenous leukaemia
Ventavis/Bayer Schering Pharma AG	Iloprost	B01AC13	synthesised from commercially available starting materials	Primary pulmonary arterial hypertension

*biotechnology-derived medicinal product

TABLE 3

Reimbursed orphan medicines in Bulgaria (with European marketing authorisation and without prior orphan designation) in Europe

Reimbursed orphan drug/ Marketing Authorisation Holder	INN	ATC code	Manufacturing method	Disease name
ANNEX 3				
Advate/Baxter AG*	Octocog alpha	B02BD02	recombinant DNA technology (rDNA)	Haemophilia A
Kogenate/Bayer*	Octocog alpha	B02BD02	recombinant DNA technology (rDNA)	Haemophilia A
Alimta/Eli Lilly Nederland B.V.	Pemetrexed	L01BA04	synthesised from commercially available starting materials	Malignant pleural mesothelioma
Tevagrastim/Teva Generics GmbH*	Fligrastim	L03AA02	recombinant DNA technology (rDNA)	Severe congenital, cyclic or idiopathic neutropenia
Erbitux/Merck KGaA*	Cetuximab	L01XC06	recombinant DNA technology (rDNA)	Squamous cell cancer of the head and neck
Ferriprox/Apotex Europe B.V.	Deferiprone	V03AC02	synthesised from commercially available starting materials	Thalassemia major
Hycamtin/SmithKline Beecham	Topotecan	L01XX17	synthesised from commercially available starting materials	Carcinoma of the ovary, small cell lung cancer
Mabcampath/Genzyme Europe B.V.*	Alemtuzumab	L01XC04	recombinant DNA technology (rDNA)	B-cell chronic lymphocytic leukaemia
Mabthera/Roche Registration Ltd.*	Rituximab	L01XC02	recombinant DNA technology (rDNA)	Follicular lymphoma, diffuse large B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia
NovoSeven/Novo Nordisk A/S*	Eptacog alpha (activated)	B02BD08	recombinant DNA technology (rDNA)	Congenital haemophilia with inhibitors to coagulation factors VIII or IX, congenital FVII deficiency, Glanzmann's thrombasthenia
Sutent/Phizer Ltd., UK*	Sunitinib	L01XE04	recombinant DNA technology (rDNA)	Unresectable and/or metastatic malignant gastrointestinal stromal tumour
Taxotere/Aventis Pharma S.A.	Docetaxel trihydrate	L01CD02	synthesised from commercially available starting materials	Metastatic gastric adenocarcinoma, squamous cell carcinoma of the head and neck
Temodal/SP Europe	Temozolomide	L01AX03	synthesised from commercially available starting materials	Glioblastoma multiforme, anaplastic astrocytoma
Velcade/Janssen-Cilag International N.V.	Bortezomib	L01XX32	synthesised from commercially available starting materials	Multiple myeloma
Xeloda/Roche Registration Ltd.	Capecitabine	L01BC06	synthesised from commercially available starting materials	Advanced gastric cancer
Zevalin/Bayer Schering Pharma*	Ibritumomab	V10XX02	recombinant DNA technology (rDNA)	Follicular lymphoma
ANNEX 4				
Humira/Abbot Laboratories Ltd.*	Adalimumab	L04AB04	recombinant DNA technology (rDNA)	Juvenile idiopathic arthritis

*biotechnology-derived medicinal product

(23) and sets up the conditions for marketing authorisation of orphan medicines, their pricing and funding. No reference is made in Bulgarian legislation to Commission Regulation (EC) No 847/2000 of 27.04.2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product. Thus no regulatory assistance is provided to the potential sponsors as intended with the Commission Regulation (EC) No 847/2000 (7), neither does a clear interpretation exist for Regulation (EC) No 141/2000 requirements at a national level.

The orphan medicines are authorised through the centralised procedure but in order to make them affordable on a national level a price need to be registered and a procedure for funding need to be regulated. Both processes are controlled by the Ministry of Health in Bulgaria.

Once included in the PDL, the 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.

Analysis of the orphan medicines included in the Bulgarian Positive Drug List

The Bulgarian Positive Drug List (19) consists of four annexes which are divided based on the sources of funding. For the purpose of this publication we studied the orphan medicines, which are included in Annexes 3 and 4 and are fully reimbursed by the state budget.

Our analysis is separated in two parts- availability of orphan medicines with European marketing authorisation and prior orphan designation in Europe, and availability of orphan medicines with European marketing authorisation and without prior orphan designation in Europe into the Bulgarian PDL.

The orphan medicines with European marketing authorisation and prior orphan designation in Europe that are included in the Bulgarian PDL are presented in **Table 2**. There are 21 orphan medicines identified (10 in Annex 3 and 11 in Annex 4), representing treatment for 6 anatomical systems, but mainly various types of leukaemia, renal cell carcinoma, mucopolysaccharidosis, acromegaly etc. It is necessary to clarify that the list with medicines also provides the list with specific diagnoses for which they are funded.

The orphan medicines with European marketing authorisation and without prior orphan designation in Europe available in Bulgarian PDL are presented in **Table 3**. We have identified 17 orphan medicines (16 in Annex 3 and 1 in Annex 4) representing treatment for diseases of 3 anatomical systems: haemophilia, thalassaemia, various types of cancer, juvenile idiopathic arthritis etc.

The relative shares of both studied groups of orphan medicines which are reimbursed in Bulgaria are presented in **Fig. 1**. In comparison with all orphan medicines centrally placed on the market only 21 out of 56 with European orphan designation and European marketing authorisation are available and funded in Bulgaria. 29% of them are biotechnology-derived. Another 17 (out of 47) orphan medicines with European marketing authorisation and without prior orphan designation in EU are reimbursed and 59% of them are biotechnology-derived. Thus approximately 37% of the orphan medicines (both with and without prior orphan designation) are available and funded in Bulgaria.

Although there are a lot of initiatives regarding the rare diseases and orphan medicines at the national level it is evident that still the Bulgarian legislation is not fully harmonised with the corresponding European documents (33). There are chapters dealing with rare diseases in the Health Act and with orphan medicines in the Law on Medicinal Products but a lot of other elements are missing as are the cooperation with marketing authorisation holders and full harmonisation with the European regulatory policy. Thus patients suffering from rare diseases are also underserved in Bulgaria (19, 25, 27).

The latter conclusion is supported by the limited availability of the orphan medicines in the Bulgarian PDL. The reasons for such a limited access could be explained with financial reasons or with the existing therapeutic practice (9, 12). Unfortunately we do not possess the patient registries for all rare diseases, as well as official information about all the patients using orphan medicines and we could not evaluate their usage and compare with other countries (27). This is a major limitation of our study. Further studies need to be done to clarify the real patient access in respect of the financial affordability of main and supporting therapy.

The fact that only 37% of all medicines with orphan designation are available in the list with reimbursed medicines is very negative and shows that a lot of efforts need to be made at the national level for ensuring better patient therapy. Evidently the centralised marketing authorisation is not supported by the following national regulatory requirements for price setting and inclusion into the PDL, which are necessary for guaranteeing medicines availability on national market. Thus we can conclude that the regulators and payers still did not ensure a balance between the needs of patients and resources allocation.

Conclusions

Although the Commission recommends that Member States put in place strategies organized around national plans for rare diseases and orphan medicines, ensuring access to high-quality healthcare, there are significant differences in orphan drug availability amongst the countries. The access to orphan medicines through the Bulgarian PDL is limited for patients with rare diseases and further studies about their affordability both for the reimbursement system and for the patients need to be done. The Bulgarian health legislation needs of further development to introduce important European requirements concerning the access to orphan medicines. The lack of national guidelines on treatment of rare diseases did not allow us to assess the availability of supportive treatment. We could recommend establishment of disease management national guidelines focused not only on orphan drugs but on patient and his/her disease including non-orphan treatment.

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