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ORPHAN DRUGS IN BULGARIA

PERIODIC REVIEW OF THE ACCESS TO ORPHAN DRUGS IN BULGARIA

Methodology

The subject of this review are the medicinal products which have been designated under the Regulation (EC) 141/2000 and have marketing authorization and positive evaluation of significant benefits.

Orphan drug is a medical product:

- **that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, OR that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;**
- **AND that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.**

The report contains 4 sections:

- ***Orphan drug designation and marketing authorization***
- ***Pricing, inclusion in the Positive drug list and reimbursement***
- ***Mechanisms for accelerated access to innovative medicines***
- ***Conclusions***

There are 2 annexes, attached to the review:

- ***List of orphan drugs in EU and Bulgaria*, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorization holder and date of marketing authorization for each item. Additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria (PDL) and if it is reimbursed by public funds.**
- ***References***

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Section 1
ORPHAN DRUG DESIGNATION AND MARKETING AUTHORIZATION

The medicinal products that have received orphan designation and marketing authorization by the European Medicines Agency (EMA) are the subject of this review. Orphan drugs are authorized for use by centralized procedure under **Regulation (EC) 726/2004 of the European Parliament and the Council of 31 March 2004**. It applies to all EU countries.

In Bulgaria, this issue is governed by the **Medicinal Products in Humane Medicine Act (MPHMA)**:

Art. 25. (1) Criteria for designating a medicinal product, intended to treat, prevent or diagnose rare diseases, are set out in Regulation (EC) 141/2000 of the European Parliament and Council.
(2) The procedure for issuing a marketing authorization for medicinal products under par. 1 is defined by Regulation (EC) 726/2004 of the European Parliament and Council.

Authorization decisions under the centralised procedure are taken *"in the interest of public health"* and *"on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations"*. This mechanism itself is one of the incentives that European authorities provide to the research pharmaceutical industry in order to develop drugs for rare diseases. They also include:

- an accelerated assessment procedure for medicines which are of essential importance to the public health and especially that represent innovation in therapeutic terms;
- advices from EMA on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in accordance with the acting European legislation on that matter;
- reduction of fees, deferring the payment of fees, taking over responsibility for translations and offering administrative assistance (according to **Art. 7 of Regulation (EC) 141/2000** a special contribution from the Community is allocated every year to EMA. It is used exclusively to waive, in part or in total, all the fees payable under the Community rules);
- market exclusivity (according to **Art. 8 of Regulation (EC) 141/2000** the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product);
- medicinal products, which are designated as orphan medicinal products, are eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.

The existence of this package of incentives is justified by the fact that most of rare diseases occur so infrequently that the costs of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product and the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions.

After a steady increase of the number of authorized orphan drugs since 2001, when the incentives for their development were enacted, since 2008 there is a kind of standstill (Diagram 1). This, together with the fact that significant proportion of newly registered orphan drugs are not actually available in all

Member States, is a possible reason to reassess the current legislation in this area at Community and national level.

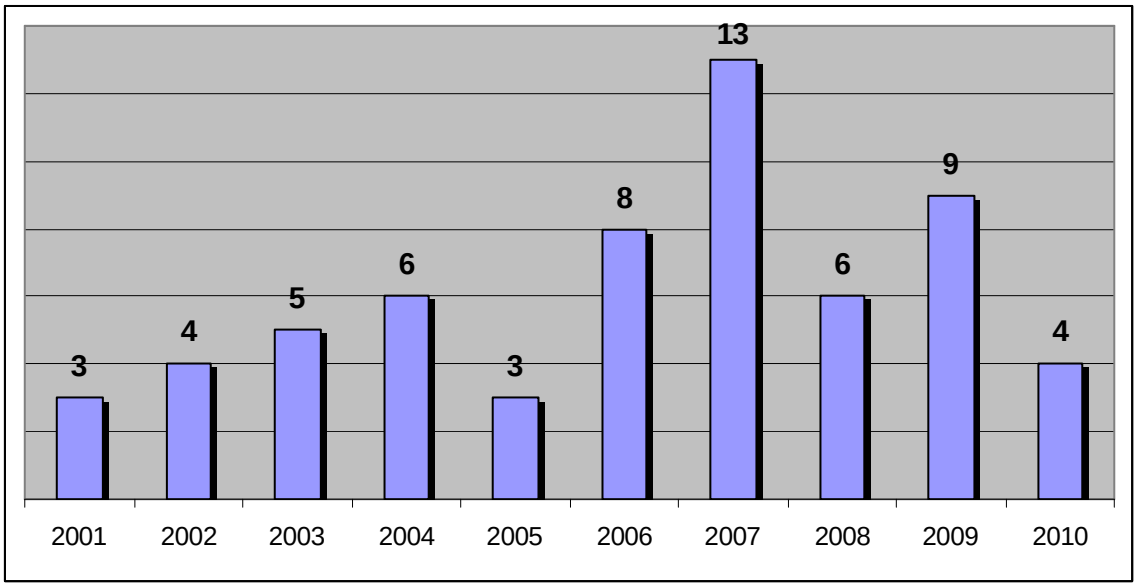

Diagram 1. Number of orphan drug market authorizations, issued by EMA per year

Currently, there are 61 authorized medical products with orphan drug designation in the European Union. Compared to our previous report from June 2010, there is no substantial change. The list contains two new orphan drugs – *Esbriet (pirfenidone)* and *Vpriv (velaglucerase alfa)*, one – *Thelin (Sitaxentan sodium)* has been withdrawn from the market due to unforeseen side effects and two others have been renamed – *Peyona (caffeine citrate)* with old trade name *Nymusa* and *Rilonacept Regeneron (rilonacept)* with old trade name *Arcalyst* (see Annex 1).

Section 2
PRICING, INCLUSION IN THE POSITIVE DRUG LIST AND REIMBURSEMENT

The second section of this review concerns the attitude of the current legislation in Bulgaria towards orphan drugs and how ultimately it provides access for patients with rare diseases to them, i.e. the reimbursement of orphan drugs by the national health system. This is a difficult and long process, starting from the negotiation of price and level of reimbursement from public funds, until finally comes the actual therapy with these drugs. Texts of the **Medicinal Products in Humane Medicine Act (MPHMA)** define the basic framework of this mechanism, but the major role is played by the relevant to MPHMA provisions of the Council of Ministers (CM) and ordinances of the Ministry of Health (MoH). MoH and the National Health Insurance Fund (NHIF) are the key authorities, spending public funds for treatment with orphan drugs.

According to MPHMA, regulation and control of prices of medicines, as well as reimbursement by public funds are core functions of health authorities:

> *Art. 258. (1) The state regulates the prices of medicines, included in the Positive drug list under Art. 262, par. 4 and paid by public funds, in accordance with the lowest reference price in the Member States.*
> *(2) The State regulates the marginal prices of medicinal products on prescription, outside those under par. 1.*

For this purpose, CM upon proposal of the Minister of Health has created the **Commission on prices of medicines** whose terms and conditions of work are defined by relevant ordinance. The pricing (negotiation of price and level of reimbursement) of orphan drugs in Bulgaria is determined by the **Ordinance on the conditions, rules and procedures for regulating and registering the prices of medicines**. Fundamental point in pricing is the principle of the lowest of reference values. The price of the medicinal product (which will be included in the **Positive Drug List (PDL)** and will be reimbursed by public funds, as that is the case of orphan drugs) is formed on the basis of producer's price, which could not be higher than the lowest price for the same product, paid by public health insurance funds in Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal and Spain. Where there is no producer's price in these countries, the price is formed in the same manner and based on the following additional reference countries – Belgium, Czech Republic, Poland, Latvia and Hungary. Fixed margins for wholesalers and retailers, as well as value added tax are added to form the final price.

Having been priced, orphan drugs can be included in the PDL. The **Commission on the PDL** examines and decides on applications for inclusion, amendments and/or exclusion of drugs from PDL.

PDL includes prescription medicines needed to cover the health needs of the population and paid with funds of:

- the NHIF budget;
- the state budget, beyond the scope of mandatory health insurance;
- the budget of the healthcare establishments under Art. 5 of the Medical-Treatment Facilities Act (MTFA);
- the budget of the medical-treatment facilities with state and/or municipal stake upon Art. 9 and 10 of MTFA.

PDL of Bulgaria groups the drugs into 4 annexes:

- Annex 1 – drugs for treatment, paid under the Health Insurance Act (HIA);

- Annex 2 – drugs paid by the budget of the medical-treatment facilities under Art. 5 of MTFA and by the budget of the hospitals with state and/or municipal stake upon Art. 9 and 10 of MTFA;
- Annex 3 – drugs for treatment outside the scope of HIA, paid in accordance with Art. 82, par. 1, item 8 of the Law on Health;
- Annex 4 – drugs for treatment of AIDS and infectious diseases.

CM upon proposal by the Minister of Health has determined in an **ordinance the conditions, rules and criteria for inclusion, amendments and/or exclusion of drugs from PDL and the terms and conditions of work of the Commission on PDL**. Under this ordinance, drugs that are candidates for inclusion, should meet the following specifications:

- authorization for use under MPHMA;
- price upon Art. 258, par. 1 of MPHMA;
- indication for treatment, prevention or diagnosis of diseases in accordance with Art. 2, par. 2 of the regulation itself;
- international non-proprietary name, to which the medicinal product belongs, is reimbursed by public funds for the same conditions or indications in at least three of the following countries: Romania, Czech Republic, Estonia, Greece, Hungary, Lithuania, Portugal and Spain;
- dosage mode and route of administration, which are suitable for treatment of those diseases;
- assessment of therapeutic value and social significance.

Until the end of 2010 orphan drugs in Bulgaria were included in Annexes 3 and 4. Since 2011, in conjunction with the new reimbursement schemes, some of them (for rare non-oncological diseases) were transferred to Annex 1 (of medicinal products for treatment, paid under HIA).

Currently, PDL of Bulgaria includes 22 orphan drugs (in Annexes 1, 3 and 4) of the 61, registered by EMA. Compared to June 2010, there is an increase of 4 new orphan drugs. This can be seen as a result of the improved awareness for rare diseases among physicians, patients and health authorities, as well as the intentions of pharmaceutical manufacturers to market their products in Bulgaria. However, the time period from receiving European marketing authorization to inclusion in PDL is still too long (see Table 1). The remaining approximately 2⁄3 of orphan drugs, registered by EMA, are virtually unavailable for patients with rare diseases in Bulgaria, given the fact, that outside the PDL, they are not subject to reimbursement from public funds. In our view, it is not because of the requirements of the Commission on PDL, but rather because of the reluctance of the producers to register price of their medicines in Bulgaria.

Regarding reimbursement of orphan drugs it should be underlined that current European regulations do not affect in any way the competences of Member States concerning pricing of medicinal products or their inclusion within the national health system or schemes of social assistance, based on health, economic or social conditions. Whether a drug will be included into the PDL of Bulgaria and will be subject to public reimbursement scheme, it depends entirely on the current regulations and perceptions of the healthcare authorities.

Starting from 2011, the reimbursement of the orphan drugs with public funds is set up by two mechanisms – under **Ordinance (MoH) 34 from 25 November 2005 on the procedure for payment from the state budget of the medical treatment of Bulgarian citizens, outside the scope of mandatory health insurance** (through MoH budget) – or – **Ordinance (MoH) 38 from 16 November 2004 on the list of conditions for which home treatment NHIF fully or partly pays the medicines, medical devices and dietary foods with special medical purposes** (through NHIF budget).

Table 1*. Time from orphan drug market authorization to PDL inclusion

Trade name	*Date of market authorization by EMA*	*Date of inclusion in PDL*	*Delay (in months)*
Afinitor	03/08/2009	09/12/2010	16 months
Elaprase	08/01/2007	24/06/2009	29 months
Evoltra	29/05/2006	09/12/2010	54 months
Exjade	28/08/2006	24/06/2009	34 months
Lysodren	28/04/2004	09/12/2010	77 months
Mozobil	31/07/2009	09/12/2010	16 months
Naglazyme	24/01/2006	24/06/2009	41 months
Nplate	04/02/2009	09/02/2010	12 months
Somavert	13/11/2002	24/06/2009	79 months
Torisel	19/11/2007	21/08/2009	21 months
Tracleer	15/05/2002	08/04/2010	95 months
		Average (± S_x):	**43 ± 29.1 months**

****Note.: The table includes only the drugs, which have been included in the new PDL after 1 June 2009.***

16 orphan drugs (from the 22 in PDL) are reimbursed at 100% (10 under Ordinance 34 and 6 under Ordinance 38) and in theory should be available for the patients with rare diseases. So, there is an increase of 5 additional orphan drugs over the previous period. These results come mainly from the increase from 1 to 3 of the reimbursed orphan drugs for primary pulmonary hypertension and the inclusion of new oncological orphan drugs.

A major shortcoming of the new framework is the longtime unsolved problem with the treatment of mucopolysaccharidosis (types I, II and VI). There is also an interesting case with *Nplate (romiplostim)*, included in Annex 4 and reimbursed under Ordinance 34 for the treatment of patients with chronic immune (idiopathic) thrombocytopenic purpura (ICD code D69.3). However, the list of diseases whose home treatment is covered by NHIF includes thrombocytopenic idiopathic purpura (ICD code D69.3) as well, so there is a conflicting regulation.

Despite the official statistics, in reality there is no dramatical improvement of the accessibility and availability of treatment for the people with rare diseases in Bulgaria. The fact that an orphan drug is included in the PDL and reimbursed under one of the two regulations, does not mean that in practice it is accessible and available in adequate quantities for each patient. Institutions for planning and funding for treatment and rehabilitation of patients with rare diseases do not have actual and reliable data on the number and distribution of patients in the country and information on the compliance and effectiveness of this expensive treatment.

Section 3
MECHANISMS FOR ACCELERATED ACCESS TO INNOVATIVE MEDICINES

For several years, mechanisms, that significantly improve access to medicinal treatment for people with rare diseases, are presented at European level. Perhaps the most famous and important of them is the compassionate use of drugs, which is already regulated and working in many countries.

This “compassionate” use is very different from the term of “palliative care”, as it is officially translated in Bulgarian. In the EU healthcare framework "compassionate use" means making a medicinal product available to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactory by an authorized medicinal product. The medicinal product concerned must either be a subject of an application for a marketing authorization in accordance with **Art. 6 of Regulation (EC) 726/2004** or must be undergoing clinical trials. So, it is assuming the hypothesis of management of patients with still unauthorized medicines. Accelerated assessment procedures for medicinal products of major therapeutic interest and procedures for obtaining temporary authorizations, subject to certain annually reviewable conditions, are set in order to meet the expectations of patients and to take account of the increasingly rapid progress of science and therapies.

At present time, **Art. 83 of Regulation (EC) 726/2004** is the only normative text in EU, which addresses the issue of compassionate use of orphan drugs by defining a common approach regarding the criteria and conditions for compassionate use of new drugs under the laws of Member States. However, the decision for such programs is at the competences of the national authorities. They can be consulted by EMA. When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted.

Such a mechanism does not exist in Bulgaria yet. There is no prospect too because of problems with financing of such programs for compassionate use of orphan drugs, which will occur. A text in MPHMA indirectly treats this issue:

> *Art. 9. (1) Treatment of specific patient can be done with a medicinal product, which is not authorized under Chapter Three, by a special order of the medical-treatment facility under conditions and procedures, specified in a ordinance by the Minister of Health.*

The established under this article **Ordinance (MoH) 2 from 10 January 2001 on the procedures for treatment with medicinal products, that are not authorized for use in Bulgaria**, regulates the use of drugs that are not authorized for use in the country, but may be prescribed, provided that are permitted for use in other countries, and which are intended to treat rare diseases, or specific indications where treatment with permitted drugs has no effect. For orphan drugs, which are approved under the centralized procedure of EMA, this ordinance has not so much sense given that they are automatically registered in all Member States, including Bulgaria. The problems with the access of Bulgarian patients to them are mainly related to the pricing and reimbursement procedures. Ordinance (MoH) 2 is related to drugs (without orphan drug designation), which are used for rare diseases and have not been registered in Bulgaria. At present, there are no provisions of the state budget for the purchase of such drugs under this order.

Section 4
CONCLUSIONS

Bulgarian rare diseases patients have real access to 16 from the 61 orphan drugs, registered in EU. Why is that? Since this review examines what happens with orphan drugs after receiving marketing authorization from EMA, the difficulties and problems in the process of their research and development won't be discussed.

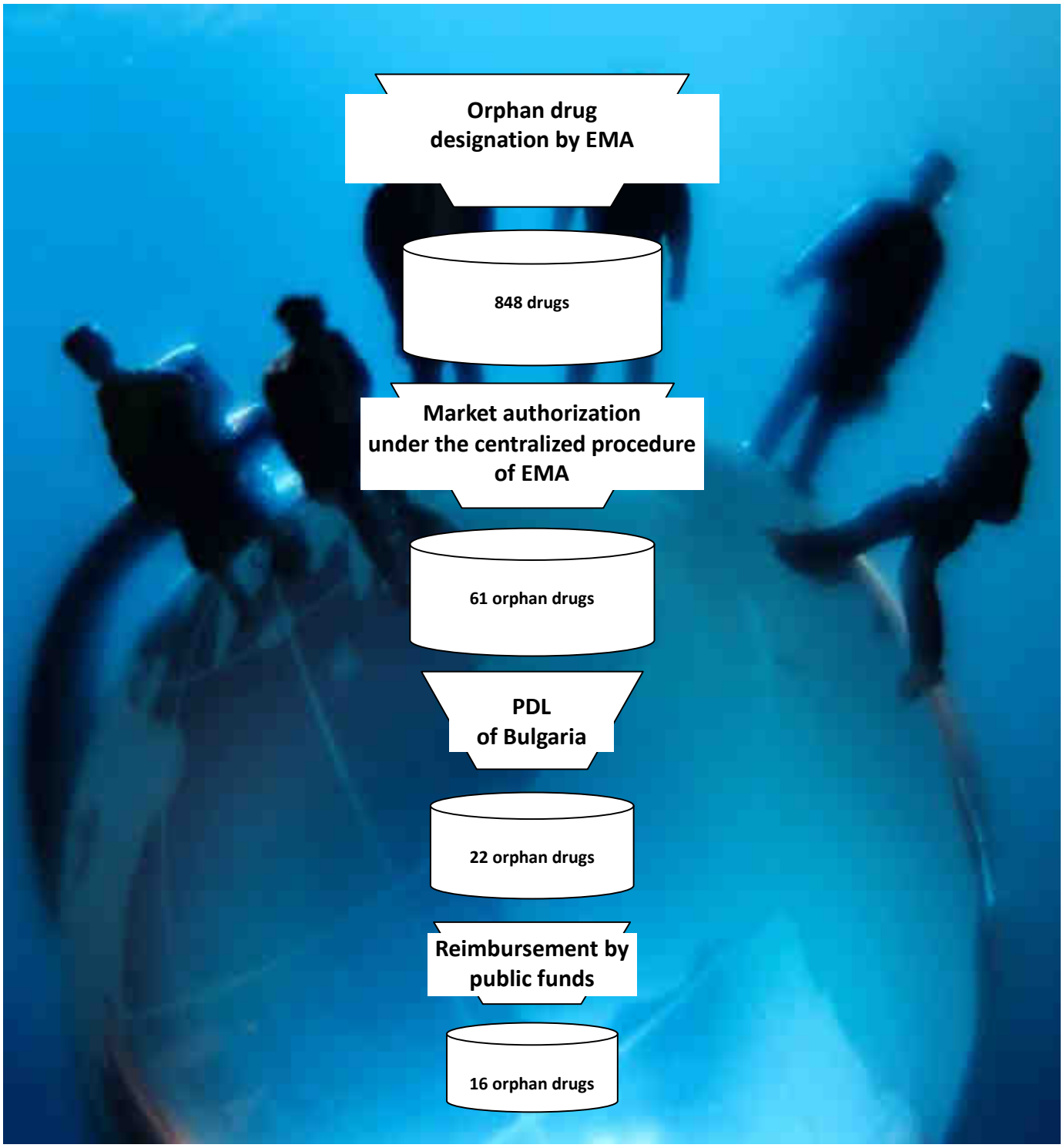

Diagram 2. Access to orphan drugs in Bulgaria (by March 2011)

During the review of the dossier of a candidate for orphan drug designation, its unique or significant therapeutic benefits over the existing therapies so far are specially underlined. The evaluation committee in EMA is aware of the possible small number of participants in the clinical trials. But even when the medicine has obtained orphan designation and centralized marketing authorization, it is often that national regulatory authorities are trying to require more data on its clinical efficacy. So, the lack of enough clinical evidence is sometimes cited as a formal reason for denial of reimbursement, as that is the case with the orphan drug for mucopolysaccharidosis type II which reimbursement in Bulgaria has been refused. The Ordinance on the conditions, rules and criteria for inclusion, amendments and/or exclusion of drugs from PDL makes no essential exception for orphan drugs (registered by the centralized procedure of EMA) and they are treated "equally" with the others. The new changes in the provision of medicinal therapy for patients with rare diseases have introduced an obligation for the Commission on pricing to provide to the Commission on PDL the working dossiers of drugs, which will be reimbursed by NHIF and MOH. This theoretically would facilitate the procedure and would shorten the time for patients to access appropriate and quality medication.

Regarding the pricing of orphan drugs, the existing mechanism with the smallest value from a set of international reference prices seriously reduces the opportunities for flexible solutions. The inclusion of the reference countries with floating euro exchange rate makes the pricing of orphan drugs depending on macroeconomic indicators in these countries and thereby allows serious fluctuations in the price. This is a specific reason for the reluctance of some companies to register prices of their orphan drugs in the small Eastern European countries like Bulgaria.

The limited information and awareness for innovative therapies and rare diseases as a whole should also be considered. This, combined with relatively young patient organizations of people with rare diseases and the small experience of medical specialists with orphan drugs, is an obstacle for placing the adequate access to orphan drugs as a priority in public health system. Society is generally poorly informed about the problem and there is no solidarity and consensus.

The combined action and correlation of all these factors lead to restrictions in access to orphan drugs, as well as long delay in their provision. Despite public comments and opinions that the financial issue is of primary importance, the share of the costs for orphan drugs from the total public spendings on medicines in countries with highly developed health systems towards the rare diseases such as France, Italy and Germany is very small.

Therefore, the most important is the presence of clear and specific sets of legal and organizational measures. For Bulgaria, these could be:

- adoption of the Clinical-added value of orphan drugs (*CAVOD*);
- identification of new, more flexible pricing and reimbursement schemes (for example, change in methodology of defining the reference price, outcomes-based reimbursement);
- support for patients associations of people with rare diseases;
- effective implementation of the National plan for rare diseases;
- establishment of reference and/or expertise centers for rare diseases;
- support for epidemiological registers and research projects on rare diseases and orphan drugs.

Only a similar set of measures, which is a joint effort of all stakeholders and takes into account all their specific capacities and needs, can lead to sustainable improvement in this area.

ANNEX 1
List of orphan drugs in EU and Bulgaria

Orphan Drugs in European Union and Bulgaria

(by trade name in alphabetical order)

Trade name	Active substance and ATC code	Indication	Marketing authorization holder	Marketing authorization date	Inclusion in PDL	Reimbursement
AFINITOR	Everolimus L01XE10	Renal cell carcinoma	Novartis Europharm	03/08/2009	YES (A2, A3)	YES (MoH, O34)
ALDURAZYME	Laronidase A16AB05	Mucopolysaccharidosis, type I	Genzyme	10/06/2003	YES (A4)	NO
ARZERRA	Ofatumumab L01XC10	B-cell chronic lymphocytic leukemia	Glaxo Group	19/04/2010		
ATRIANCE	Nelarabine L01BB07	T-cell acute lymphoblastic leukemia T-cell lymphoblastic lymphoma	GlaxoSmithKline Research & Development	22/08/2007	YES (A2, A3)	YES (MoH, O34)
BUSILVEX	Busulfan L01AB01	Hematopoietic progenitor cell transplantation	Pierre Fabre Médicament	09/07/2003		
CARBAGLU	N-carbamyl-L-glutamic acid A16AA05	Hyperammonemia due to N-acetylglutamate synthase deficiency	Orphan Europe	24/01/2003		
CAYSTON	Aztreonam J01DF01	Cystic fibrosis	Gilead Sciences International	21/09/2009		
CEPLENE	Histamine dihydrochloride L03AX14	Acute myeloid leukemia	EpiCept	07/10/2008		
CYSTADANE	Betaine anhydrous A16AA06	Homocystinuria	Orphan Europe	15/02/2007		
DIACOMIT	Stiripentol N03AX17	Severe myoclonic epilepsy	Biocodex	04/01/2007		
ELAPRASE	Idursulfase A16AB09	Mucopolysaccharidosis, type II (Hunter syndrome)	Shire Human Genetic Therapies	08/01/2007	YES (A4)	NO
ESBRIET	Pirfenidone L04AX05	Idiopathic pulmonary fibrosis	InterMune Europe	28/02/2011		
EVOLTRA	Clofarabine L01BB06	Acute lymphoblastic leukemia	Bioenvision	29/05/2006	YES (A2, A3)	YES (MoH, O34)
EXJADE	Deferasirox V03AC03	Chronic iron overload (in beta thalassemia patiens)	Novartis Europharm	28/08/2006	YES (A1, A2)	YES (NHIF, O38)
FABRAZYME	Agalsidase beta A16AB04	Fabry disease	Genzyme	03/08/2001	YES (A1)	YES (NHIF, O38)

FIRAZYR	Icatibant acetate C01EB19	Hereditary angioedema	Jerini	11/07/2008		
FIRDAPSE	Amifampridine N07XX05	Lambert-Eaton myasthenic syndrome	EUSA Pharma	23/12/2009		
GLIOLAN	5-aminolevulinic acid hydrochloride L01XD04	Malignant glioma	Medac Gesellschaft für klinische Spezialpräparate	07/09/2007		
GLIVEC	Imatinib mesilate L01XE01	Chronic myeloid leukemia Acute lymphoblastic leukemia Myelodysplastic/myeloproliferative diseases Hypereosinophilic syndrome Chronic eosinophilic leukemia Gastrointestinal stromal tumours Dermatofibrosarcoma protuberans	Novartis Europharm	07/11/2001	YES (A2, A3, A4)	YES (MoH, O34)
ILARIS	Canakinumab L04AC08	Cryopyrin-associated periodic syndromes	Novartis Europharm	23/10/2009		
INCRELEX	Mecasermin H01AC03	Primary insulin-like growth factor 1 deficiency (Laron syndrome)	Tercica Europe	03/08/2007		
INOVELON	Rufinamide N03AF03	Lennox Gastaut syndrome	Eisai	16/01/2007		
KUVAN	Sapropterin dihydrochloride A16AX07	Hyperphenylalaninemia	Merck	02/12/2008		
LITAK	Cladribine L01BB04	Hairy cell leukemia	Lipomed	14/04/2004	YES (A2, A3)	YES (MoH, O34)
LYSODREN	Mitotane L01XX23	Adrenal cortical carcinoma	Laboratoire HRA Pharma	28/04/2004	YES (A2, A3)	NO
MEPACT	Mifamurtide L03AX15	Osteosarcoma	IDM Pharma	06/03/2009		
MOZOBIL	Plerixafor L03AX16	Lymphoma Multiple myeloma Hematopoietic stem cell transplantation	Genzyme Europe	31/07/2009	YES (A2, A3)	NO
MYOZYME	Recombinant human acid alpha glucosidase A16AB07	Glycogen storage sisease, type II (Pompe disease)	Genzyme Europe	29/03/2006	YES (A4)	NO
NAGLAZYME	N-acetylgalactosamine-4- sulfatase A16AB08	Mucopolysaccharidosis, type VI (Maroteaux-Lamy syndrome)	BioMarin Europe	24/01/2006	YES (A4)	NO

NEXAVAR	Sorafenib L01XE05	Hepatocellular carcinoma Renal cell carcinoma	Bayer Healthcare	19/07/2006	YES (A2, A3)	YES (MoH, O34)
NPLATE	Romiplostim B02BX04	Immune (idiopathic) thrombocytopenic purpura	Amgen Europe	04/02/2009	YES (A2, A4)	YES (MoH, O34)
ONSENAL	Celecoxib L01XX33	Familial adenomatous polyposis	Pharmacia-Pfizer	17/10/2006		
ORFADIN	Nitisinone A16A X04	Tyrosinemia, type 1	Swedish Orphan International	21/02/2005		
PEDEA	Ibuprofen C01EB16	Patent ductus arteriosus	Orphan Europe	29/07/2004		
PEYONA	Caffeine citrate N06BC01	Primary apnea	Chiesi Farmaceutici	02/07/2009		
PHOTOBARR	Porfimer sodium L01XD01	Barrett's Oesophagus	Axcan Pharma International	25/03/2004		
PRIALT	Ziconotide N02BG08	Chronic pain who require intrathecal analgesia	Elan Pharma In-ternational	21/02/2005		
REPLAGAL	Agalsidase alfa A16AB03	Fabry Disease	TKT UK	03/08/2001		
REVATIO	Sildenafil citrate G04BE03	Pulmonary arterial hypertension	Pfizer	28/10/2005	YES (A1)	YES (NHIF, O38)
REVLIMID	Lenalidomide L04AX04	Multiple myeloma	Celgene Europe	14/06/2007		
REVOLADE	Eltrombopag B02BX05	Immune (idiopathic) thrombocytopenic purpura	Glaxo-SmithKline Trading Services	11/03/2010		
RILONACEPT REGENERON	Rilonacept L04AC08	Cryopyrin-Associated Periodic Syndromes	Regeneron UK	23/10/2009		
SAVENE	Dexrazoxane V03AF02	Anthracycline extravasation	TopoTarget	28/07/2006		
SIKLOS	Hydroxycarbamide L01XX05	Sickle cell syndrome	OTL Pharma	29/06/2007		
SOLIRIS	Eculizumab L04AA25	Paroxysmal nocturnal hemoglobinuria	QuadraMed	20/06/2007		
SOMAVERT	Pegvisomant H01AX01	Acromegaly	Pfizer	13/11/2002	YES (A1, A2)	YES (NHIF, O38)

SPRYCEL	Dasatinib L01XE06	Chronic myeloid leukemia Acute lymphoblastic leukemia	Bristol-Myers Squibb Pharma	20/11/2006	YES (A2, A3)	YES (MoH, O34)
TASIGNA	Nilotinib L01XE08	Chronic myeloid leukemia	Novartis Europharm	19/11/2007	YES (A2, A3, A4)	YES (MoH, O34)
TEPADINA	Thiotepa L01AC01	Transplantation of hematopoietic progenitor cells	ADIENNE	15/03/2010		
THALIDOMIDE CELGENE	Thalidomide L04AX02	Multiple myeloma	Celgene Europe	16/04/2008		
TORISEL	Temsirolimus L01XE09	Renal cell carcinoma Mantle cell lymphoma	Wyeth Europa	19/11/2007	YES (A2, A3)	YES (MoH, O34)
TRACLEER	Bosentan monohydrate C02KX01	Pulmonary arterial hypertension	Actelion	15/05/2002	YES (A1)	YES (NHIF, O38)
TRISENOX	Arsenic Trioxide LO1XX27	Acute promyelocytic leukemia	Cell Therapeutics (UK)	05/03/2002		
VENTAVIS	Iloprost B01AC11	Primary pulmonary hypertension	Bayer Schering	16/09/2003	YES (A1, A2)	YES (NHIF, O38)
VIDAZA	Azacitidine L01BC07	Myelodysplastic syndromes Chronic myelomonocytic leukemia Acute myeloid leukemia	Celgene Europe	17/12/2008		
VOLIBRIS	Ambrisentan CO2KX02	Pulmonary arterial hypertension	Glaxo Group	21/04/2008		
VPRIV	Velaglucerase alfa A16AB10	Gaucher disease, type 1	Shire Pharmaceuticals Ireland	26/08/2010		
WILZIN	Zinc acetate dihydrate A16AX05	Wilson disease	Orphan Europe	13/10/2004		
XAGRID	Anagrelide Hydrochloride L01XX35	Essential thrombocythaemia	Shire Pharmaceuticals Development	16/11/2004		
YONDELIS	Trabectedin L01CX01	Advanced soft-tissue sarcoma Ovarian cancer	Pharma Mar	17/09/2007		
ZAVESCA	Miglustat A16AX06	Gaucher disease, type 1 Niemann-Pick disease, type C	Actelion	20/11/2002		

ANNEX 2
References

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  http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf
- **European Commission, DG SANCO**
  Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:EN:PDF
- **European Medicines Agency**
  Register of medicinal products
  (http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124&jsenabled=true)
- **European Medicines Agency**
  Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) No 726/2004
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf
- **Medicinal Products in Human Medicine Act**
  http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=380&categoryid=2996
- **Council of Ministers**
  Ordinance on the conditions, rules and procedures for regulating and registering the prices of medicines
  http://www.lex.bg/bg/laws/ldoc/2135573293
- **Council of Ministers**
  Ordinance on the conditions, rules and criteria for inclusion, amendments and/or exclusion of drugs from PDL and the terms and conditions of work of the Commission on PDL
  http://www.lex.bg/bg/laws/ldoc/2135574508
- **Ministry of Health**
  Positive drug list of Bulgaria
  http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=384&categoryid=1355
- **Ministry of Health**
  Ordinance (MoH) 2 from 10 January 2001 on the procedures for treatment with medicinal products that are not authorized for use in Bulgaria
  http://www.lex.bg/bg/laws/ldoc/-549188096
- **Ministry of Health**
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- **Ministry of Health**
  Ordinance (MoH) 38 from 16 November 2004 on the list of conditions for which home treatment

NHIF wholly or partly pays the medicines, medical devices and dietary foods with special medical purposes
http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=391&currentPage=4&categoryid=3151

- **Ministry of Health**
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  http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=449&categoryid=3193
- **National Health Insurance Fund**
  NHIF requirements for provision of drugs to treat rare diseases in outpatient care
  http://www.nhif.bg/web/guest/150
- **Information Centre for Rare Diseases and Orphan Drugs**
  Review of the access to medicines for rare diseases in Bulgaria, issue 1 / June 2010
  http://raredis.org/pub/OD%20Report%2022072010%20EN.pdf