

2014 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



STATE OF THE ART OF RARE DISEASE ACTIVITIES IN BULGARIA

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The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action can be found at www.eucerd.eu.

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ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2013. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the Commission Expert Group on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2013

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and a selected bibliography and list of persons having contributed to the report.

The present document contains the information from Parts II and V of the report concerning Bulgaria. A list of contributors to the report and selected sources are in annex of this document. For more information about the elaboration and validation procedure for the report, please refer to the general introduction of the main report.

Each year, there are around 15 000 downloads of the different sections of the report combined.

RARE DISEASE ACTIVITIES IN BULGARIA

Definition of a rare disease

Stakeholders in Bulgaria accept the definition of a prevalence of no more than 5 in 10 000 individuals. This definition is officially stated in the Bulgarian National Plan for Rare Diseases, and it is also included in the provisions of the Health Act.

National plan/strategy for rare diseases and related actions

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013). The Bulgarian National Plan for Rare Diseases started on 1 January 2009 and lasted for 5 years. The Plan consists of nine priorities targeting all rare diseases:

- Collection of epidemiological data for rare diseases in Bulgaria by creation of a national register;
- Improvement of the prevention of genetic rare diseases by enlarging the current screening programmes;
- Improvement of the prevention and diagnostics of genetic rare diseases by introducing new genetic tests, decentralisation of the laboratory activities and easier access to medico-genetic counselling;
- Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families;
- Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases;
- Feasibility study on the necessity, possibility and criteria for the creation of a reference centre for rare diseases of functional type;
- Organisation of a national campaign to inform society about rare diseases and their prevention;
- Support and collaboration with NGOs and patient associations for rare diseases;
- Collaboration with the other EU members.

A National Consulting Council on Rare Diseases (NCCRD) was established by the Ministry of Health, to supervise the progress and implementation of the plan. NCCRD includes medical professionals, Ministerial representatives and a representative of the National Alliance of People with Rare Diseases. Although the initial budget of the Plan was €11.3 million, subsequent funds assigned were much less and were mostly directed to genetic testing and screening activities. The National Health Insurance Fund (NHIF) reimburses rare disease treatments, while the Ministry of Health is funding some services like prenatal and neonatal screening for rare diseases. The Ministry of Health is also providing funds for treatment abroad and transplantations through subordinated national agencies, although these are not rare disease-specific bodies.

The Plan officially ended on 31 December 2013. Before that, the Ministry of Health had established a working group to prepare a draft for a Second National Plan. The Plan is expected to work closely with the National Rare Disease Registry and the centres of expertise for rare diseases, both of which are supposed to be officialised by the end of 2014. However, no schedule for the adoption and the implementation of the Second Plan was available by the end of 2013.

Starting in 2010, the year in which a EUROPLAN National Conference was held^{1,2}, annual rare diseases conferences are organised by the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD), gathering all national rare diseases stakeholders to discuss topics of common interests. The event in 2011 focused on registries for rare diseases, while 2012 and 2013 events covered centres of expertise for rare diseases.

Centres of expertise

Significant progress was achieved in 2013 regarding the centres of expertise for rare diseases in Bulgaria. The National Assembly voted amendments in the Health Act (Article 144a), requiring the Minister of Health to adopt a regulation, which will establish a National Registry for Rare Diseases, as well as will determine the criteria for designation of centres of expertise for rare diseases. The Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and

¹ <http://www.conf2010.raredis.org/>

² http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Bulgaria_n%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf

reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation. The draft regulation also envisages the establishment of a permanent National Rare Diseases Council to the Ministry of Health, as well as an official list of rare diseases. The draft was discussed at several meetings, including the National Conference for Rare Diseases in September 2013. The final draft was submitted to the Ministry of Health early in 2014. This legislation is expected to be approved by the Ministry of Health and to come into force by the end of 2014.

Despite the lack of official designation for the moment there are several academic centres that are specialised as centres of research, treatment and management for rare diseases, i.e. cystic fibrosis, mucopolysaccharidosis, thalassemia major, Gaucher disease, neuromuscular diseases, Wilson disease, porphyrias, primary immunodeficiency. Treatment with orphan medicinal products is currently reimbursed in these centres, which also manage the provision of very expensive orphan medicinal products. Medical experts from these centres also participate in developing protocols for the National Health Insurance Fund, which serve the treatment of rare disease patients.

In addition, since May 2009, the Bulgarian Association for Promotion of Education and Science (BAPES) runs highly specialised medical centre for rehabilitation and education of people with rare diseases "RareDis". Since September 2013, RareDis and ICRDOD were merged into the Institute for Rare Diseases (IRD), together with the newly-established Centre for Health Technology Assessment and Analyses (CAHTA).

Registries

The first priority in the National Plan was to provide epidemiological data on rare diseases in Bulgaria through the establishment of a National Registry. The Registry's tasks included:

- Collecting, summarising, and providing epidemiologic information on the incidence and prevalence of rare diseases in Bulgaria;
 - Assisting the preparation of diagnostic and therapeutic protocols and standards for treatment of rare diseases;
 - Assisting the Ministry of Health, the Ministry of Labour and Social Policy, and the National Health Insurance Fund in the planning and delivery of expensive treatment and medical care to patients with rare diseases;
 - Improving the interaction between health services and patient organisations;
 - Providing and publishing data needed for planning and comparison on a regional and national level.
- However, during the National Plan (2009 – 2013), no National Registry was established.

The idea to implement a National Registry for Rare Diseases re-emerged in 2013. This was motivated by the upcoming implementation of the centres of expertise for rare diseases in the country. Initial plans suggest that the Registry will collect data from these centres and prepare annual reports on rare disease epidemiology. Thus, the Registry will contain only data for rare diseases, for which there are officially designated centres of expertise. However, by the end of 2013 it is not yet decided which institution will coordinate and manage the Registry.

Despite the lack of an official National Registry, Bulgaria has recently gained a considerable amount of experience and knowledge on rare disease epidemiology. ICRDOD released a report³ in 2012 listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country. Eight nation-wide epidemiological registries concerning rare diseases were identified: the National registry of Patients with Phenylketonuria, the National Registry of Patients with Primary Immunodeficiencies (PID), the National Registry of Patients with Thalassemia Major, the National Registry of Chronic Myeloid Leukaemia Patients, the National Registry of Crohn Disease Patients, the National Registry of Wilson Disease Patients, the National Registry of Gaucher Disease Patients, the National Registry of Mucopolysaccharidosis type 2 Patients. In 2013 ICRDOD established two new registries – for primary myelofibrosis and neuroendocrine tumours.

Neonatal screening policies

One of the national plan's priorities was to improve the availability and accessibility of the current screening programs. In 1979 mass neonatal screening was introduced in Bulgaria for phenylketonuria, galactosaemia (discontinued in 1993), congenital hypothyroidism and congenital adrenal hyperplasia. Some selective metabolic screening programmes are coordinated by the University Maternity Hospital National Genetic Laboratory in Sofia for the metabolic screening programmes (phenylketonuria), and the University Paediatric Hospital in Sofia for the endocrine screening programmes (congenital hypothyroidism and congenital adrenal

³ http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf

hyperplasia). There is coverage of the entire country with more than 130 neonatal structures carrying out blood sampling 3-5 days after birth. Over 90% of neonates are included in existing measures. Ordinance 26 2007 of the Ministry of Health provides equal access to the neonatal screening programmes. However, there exist certain problems, such as postponed mailing of screening cards to centralised labs, and the need for technological upgrades.

It is expected that with the implementation of the Ministry of Health regulation on centres of expertise for rare diseases, the neonatal screening laboratories will be designated as centres of expertise as well, and they will be organised into a reference network.

Genetic testing

National guidelines for performance of genetic testing in Bulgaria are regulated by the Health Act and the National Medical Genetics Standard. Genetic tests for the diagnosis of rare diseases are provided mainly by the National Genetic Laboratory (NGL). NGL is a national reference laboratory that provides methodological guidance and control over the activities of the genetic laboratories and performs centralised some specialised tests. It was established more than 35 years ago, by initiating of biochemical analysis for some rare disorders and mass neonatal screening for PKU. At the moment NGL provides routine diagnosis with DNA analysis (including prenatal and evaluation of carrier status) for many disorders: cystic fibrosis, phenylketonuria, Wilson disease, neuromuscular disorders, Niemann–Pick (in target population), beta thalassemia, galactokinase deficiency (in target population), microdeletions and microduplications syndromes, inborn hypothyroidism and other. The NGL also has the capacity to perform routine enzymatic analysis and GS/MS analysis for diagnosis of many rare disorders (Krabe, Pompe, MPS). In 2010 the laboratory introduced MS/MS analysis for metabolic study of inherited disorders.

The government organises support of testing by financing diagnostic kits and consumables. Genetic testing abroad is possible for diseases for which genetic tests are not available in Bulgaria, after commission approval. Furthermore, clinical centres, as well as separate research teams have the opportunity through research funded projects by relevant universities and the Ministry of Education's Research Fund to apply for routine implementation of molecular genetic diagnosis for certain rare diseases. In these cases, patients' diagnosis is provided free of charge.

Diagnostic tests are registered as available in Bulgaria for 34 genes and an estimated 84 diseases in the Orphanet database⁴.

National alliances of patient organisations and patient representation

The National Alliance of People with Rare Diseases (NAPRD) in Bulgaria is an umbrella organisation of more than 30 rare disease patient associations and groups. It aims to create a link between the people with rare diseases and the representatives of the social and healthcare system. NAPRD advocates for the right to timely and equal medical care, as well as for the creation of adequate laws in the field of the protection of the rights of people with rare diseases. A NAPRD representative is also a member of National Consulting Council on Rare Diseases at The Ministry of Health.

Sources of information on rare diseases and national help lines

Orphanet activities in Bulgaria

Since 2004 there is a dedicated Orphanet team in Bulgaria, currently hosted by the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD). This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database.

Official information centre for rare diseases

ICRDOD⁵ is a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES⁶) – a non-government non-profit organisation, registered under the Bulgarian law on non-profit legal in 2003. ICRDOD is a free educational and informative service in Bulgarian and English, providing personalised replies to requests from patients, families and medical professionals. It operates a multilingual website (www.raredis.org) and a rare disease help line - (+359) 32 57 57 97. The ICRDOD also provides a bi-monthly newsletter⁷ ("Rare Diseases & Orphan Drugs"): every issue contains a cover story with an interview, news and announcements and

⁴ Information extracted from the Orphanet database in February 2014.

⁵ <http://www.raredis.org/>

⁶ http://www.raredis.org/?page_id=2147&mel=8&smel=81&lang=en

⁷ http://www.raredis.org/?page_id=2311&mel=7&smel=71&lang=en

a rare diseases reading list. It is electronic and distributed free of charge. The newsletter is published in two versions – Bulgarian (ISSN 1314-3581) and English (ISSN 1314-359X). The ICRDOD also provides an online registry of rare diseases patients, and a Rare Diseases Library in Bulgarian.

In 2010 ICRDOD started publishing reviews on rare diseases topics. These papers' objective is to summarise important information on particular topics in the field and to present it in a reader-friendly format.

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria⁸. The report contains 4 sections: orphan medicinal product designation and marketing authorisation; 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 medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

The Bulgarian Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) released a report in 2012⁹ listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country.

Help line

ICRDOD provides a rare disease help line - (+359) 32 57 57 97 providing personalised replies to requests from patients, families and medical professionals. ICRDOD is a member of EURORDIS-led European Network of Rare Diseases Help Lines and took part in the Network's Caller Profile Analysis 2011, 2012 and 2013.

Other sources of information

Departments of Medical Genetics at all University Hospitals and the National Genetic Laboratory also provide information.

Guidelines

Currently, there are no official good practices guidelines for rare diseases in Bulgaria. The Ministry of Health's medical specialty standards and NHIF's clinical pathway protocols are considered as official best practice guidelines. Nevertheless, they are general ones and do not focus on rare diseases as whole.

Medical societies tend to prepare and adopt guidelines for specific diseases, including rare diseases. These guidelines take into account leading European and international best practices guidelines, thus increasing the quality of health care for rare diseases provided in Bulgaria.

Currently, there are no specific emergency guidelines for rare diseases in Bulgaria.

Training and education initiatives

Bulgarian rare diseases stakeholders are active in promoting EU rare policy at local and regional level. The country hosted the First Rare Diseases Summer School for Health Authorities and Legislators¹⁰, an event designed to raise awareness of rare diseases among Eastern European health authorities and legislators. The event was successfully organised again in 2012 and 2013 in Greece and Turkey respectively. This initiative is a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations "Genetics" (Russia) and the Italian National Centre for Rare Diseases (CNMR). School participants come from a wide range of public fields – legislative bodies and health authorities, medical institutions, academia. The week-long event covers a variety of topics.

BAPES also traditionally organises an annual two-day rare disease training seminar for medical students. Medical students have the chance to get acknowledged with the main rare diseases concepts, such definition, major problems, important initiatives, etc. Similar events have been initiated by various patient organisations in 2013, as patients try to raise the awareness of and improve knowledge on particular rare diseases among students. Healthcare institutions and academia largely support these initiatives, holding frequent workshops for rare diseases.

⁸ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

⁹ http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf

¹⁰ http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf

National rare disease events in 2013

Rare Disease Day was marked on 28 February 2013 with events organised by the National Alliance of People with Rare Diseases¹¹. A series of information, education and charity events took place with a balloon launch in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled "Communication and Support to Patients, Based on Modern Technologies" was held in April in Sofia. Outside of Sofia, a series of rare diseases events were organised in the towns of Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

The 4th Annual Conference on Rare Diseases and Orphan Drugs was organised on 13-14 September 2013 in Plovdiv¹². The First National Conference on Rare Diseases for Medical Students was held in parallel, bringing together more than 130 students from medical universities across Bulgaria and neighbouring countries..

Hosted rare disease events in 2013

The Bulgarian Association for Promotion of Education and Science launched and organised in 2005, 2006, 2008 and 2009, the annual "Eastern European Conference on Rare Diseases and Orphan Drugs". In 2010 for the very first time the event was hosted and co-organised outside Bulgaria, in Saint Petersburg, Russia, in conjunction with the first All-Russian Conference for Rare Diseases and Rarely Used Medical Technologies. It has proved to be an efficient strategy to foster rare diseases progress in Eastern Europe. In 2011, the sixth edition¹³ of this initiative was held and co-organised in Istanbul, Turkey. BAPES acted as a co-organiser of the International Conference on Rare Diseases (ICORD) in 2013, an event that was held on October 31 – November 2 in St. Petersburg, Russia. The Bulgarian National Alliance of People with Rare Diseases initiated and organised a Balkan patient meeting on 24 March 2012 in Sofia and again on 20-21 April 2013. Leading rare diseases experts and patients from Balkan countries took part in this event.

Research activities and E-Rare partnership

National research activities

In Bulgaria, there is no specific call for rare diseases at the national fund for research, although rare disease related projects can apply. The National Plan does not envisage any official policies to stimulate research on rare diseases; it only envisages encouraging partnerships.

Participation in European research projects

A team in Bulgaria participates in 1 of the FP7 rare disease related projects.

E-Rare

Bulgaria is not currently a partner of E-Rare.

IRDiRC

Bulgarian funding agencies have not yet committed national funding to the IRDiRC.

Orphan medicinal products

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria¹⁴. The report contains information on important orphan medicinal products activities and explained how they are set up in Bulgaria in 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; and conclusions.

Orphan medicinal product committee

There is currently no orphan medicinal products specialised committee in Bulgaria. Orphan medicinal products are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. In order to optimise these procedures, in 2011 the two commissions were merged into a single one under the Ministry of Health. Subsequently, the Parliament adopted in 2012 new legislation, by which a National Council for Pricing and Reimbursement of Medicinal Products replaced the Commission at the beginning of 2013. The new body has a status of a State agency and is responsible for both pricing and

¹¹ <http://rare-bg.com/>

¹² www.conf2013.raredis.org

¹⁴ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

¹⁴ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

reimbursement of all medicinal products. Medicinal products' safety is monitored by the Bulgarian Drugs Agency.

Orphan medicinal product incentives

No specific activity reported.

Orphan medicinal product market availability situation

While the decision of market authorisation for orphan drugs is taken at European level by EMA, national authorities regulate access to these medicinal products at national level. The reimbursement decision-making procedure includes pricing and inclusion in the Positive Drug List (PDL). Medicinal products, listed in PDL's Appendix 1 (Medicinal products for treatment of conditions which is paid under the Health Insurance Act) are covered by the National Health Insurance Fund (NHIF) and those, listed in PDL's Annex 2 – by the hospitals' budget under Articles 5, 9 and 10 of the Medical Establishments Act.

There were no significant changes in medicinal product reimbursement legislation in 2013. By 2013, PDL of Bulgaria includes one (1) orphan drug in Appendix 1, seven (7) in Appendix 2, and ten (10) in both Appendices. These include: Elaprase, Evoltra, Exjade, Litak, Lysodren, Mozobil, Myozyme, Nexavar, Nplate, Revatio, Sprycel, Tasigna, Tobi Podhaler, Torisel, Ventavis, Volibris, Vyndaqel, and Yondelis.

Despite the recent increase of these figures, institutions dealing with planning and funding for treatment and rehabilitation of patients with rare diseases still 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. A recent cross-sectional observational study¹⁵ appearing in the journal *Health Policy* evaluated the conditions that impact orphan drug availability in Bulgaria and other Eastern European countries. The authors observe that in Bulgaria: *"All the other orphan drugs, being not reimbursed, are practically inaccessible for the individual patients because of their high price. Despite the increasing number of orphan drugs, which are being reimbursed in Bulgaria, in reality there is no significant improvement of the accessibility of treatment for rare diseases. Neither a national epidemiological registry nor expert centres for rare diseases exist. Regulation of alternative access to orphan drugs (e.g., compassionate use, off-label use) is also missing. In these conditions many patients are left without correct diagnosis, adequate treatment, follow-up and rehabilitation."* The system for determining pricing is proving detrimental to orphan drug availability. Bulgaria uses a history-based budget through which funds for orphan drug treatments are allocated annually based on the previous year's calculated needs. Thus if the population of newly diagnosed patients grows, medicinal treatment shortages and access limitations also increase. The inclusion of new drugs in the country's reimbursement scheme results from improved awareness for rare diseases among physicians and patient associations, as well as the intentions of pharmaceutical manufacturers to market their products in Bulgaria. The authors outline the flaws with the current EU pricing system: *"In Bulgaria, the mechanism of smallest value from a set of international reference prices reduces the opportunities for flexible solutions. The inclusion of reference countries with floating euro exchange rate makes the pricing of orphan drugs dependent on the macroeconomic indicators in these countries and thereby allowing serious fluctuations of 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 non-Eurozone countries. Financial difficulties in one country may lead to lower prices in all referring ones. It should be also underlined that Member State authorities have little negotiating leverage since these medicines have no therapeutic alternative"*. Another important element that negatively impacts small countries is a lack of clinical data around the cost-effectiveness of rare disease medicinal products. Epidemiological rare disease registries are needed to improve knowledge in this area. Thus the authors call for a reformed orphan drug policy-making process that is transparent, and based on a convergence of medical, economic, ethical and social elements.

A new study published in 2013 further concluded that the current reimbursement decision-making framework in Bulgaria is too generalised and not sufficiently transparent. It is unable to precisely assess innovative health technologies. Authors gave as an example the official criteria for inclusion into PDL (which is a must for reimbursement). These were reorganised into an assessment scoring system with decision-making criteria (presence of therapeutic alternative, clinical effectiveness, safety, pharmacoeconomics and societal value) divided into weighted indicators. A medicinal product must score 60 points at least to be included in PDL. Under the currently defined reimbursement decision-making criteria a hypothetical middle- of-the-road scenario planning shows that an orphan drug would score 20 points for therapeutic alternative, 28 for clinical effectiveness and 12 for safety. It would take no points for pharmacoeconomics and societal value. This leaves

¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22939047>

the orphan drugs with a total score of 60 points, making the final outcome of real-life assessment and decision-making heavily dependent on small fluctuations, thus, endangering patients' access to timely treatment.¹⁶

Orphan medicinal product pricing policy

There is no specific orphan medicinal product pricing policy and orphan medicinal products are subject to the general conditions as any other medicaments. The negotiation of price and level of reimbursement of orphan medicinal products in Bulgaria is determined by the Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers), and it is based on reference pricing, using data from Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal, Italy, Finland, Denmark, Slovenia, Spain, Belgium, Czech Republic, Poland, Latvia and Hungary.

Orphan medicinal product reimbursement policy

There is no specific orphan medicinal product reimbursement policy and orphan medicinal products are subject to the general conditions as any other medicaments. Medicinal products' reimbursement is regulated on national level by two legal acts – Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers) and Ordinance 38 of the Minister of Health (on the list of diseases, whose outpatient treatment is covered by the National Health Insurance Fund, NHIF). To be accessible, orphan drugs have to be priced and included in PDL, as well as their indicated medical condition has to be in the NHIF list of diseases according to Ordinance 38.

Other initiatives to improve access to orphan medicinal products

The Centre for Health Technology Assessment and Analyses (CAHTA) officially started activities in September 2013. CAHTA currently operates as an independent unit within the Institute of Rare Diseases in Plovdiv, Bulgaria.

The idea behind the establishment of CAHTA is to complement the current activities of the Institute by covering the increasingly dynamic field of health technology assessment (HTA). Introducing and applying the HTA concept in Bulgaria will allow for more transparency, objectivity and efficiency in the health system. HTA is greatly important in the field of rare diseases and orphan drugs. The extended life expectancy and improved quality of life for patients with rare diseases are the most important outcomes of all rare disease policies. These two directly depend on the timely access to advanced diagnostic and therapeutic health technologies. Proper and reliable assessment of innovative health technologies is not only important for rare diseases – it is crucial for the overall effectiveness of the entire health care system in Bulgaria.

In October 2013 CAHTA co-organised a public lecture and discussion on HTA prospects for Bulgaria at the Medical University of Plovdiv. Professor Ken Stein (University of Exeter Medical School, UK), Dr Edmund Jessop (National Health System England, UK) and Dr. Domenica Taruscio (Istituto Superiore di Sanità, Italy) were guest speakers and moderators. The discussion was followed by a training workshop on HTA on 5 October for all interested stakeholders.

Other therapies for rare diseases

No information reported.

Orphan devices

No information reported.

Specialised social services

Respite care services and therapeutic recreational programmes are provided in certain medical centres in Bulgaria and are partially reimbursed by the National Health Insurance Fund.

In Bulgaria, there are currently no specialised programmes for people for rare diseases: these patients are forced to seek alternatives in the existing general schemes for the rehabilitation and integration of people with disabilities which do not often meet European standards and recommendations in the area. They are unevenly distributed across the country and public awareness of these services is low. In addition, rare disease patients may be denied access as the Territorial Expert Medical Commission's legislation is not adapted to the specificities of rare disease. As such, one of the priorities of the National Plan is to work on an integrative approach and specialised programmes for physical and social rehabilitation of rare disease patients, however

¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/24712287>

no progress has been made to date, and patients feel that specialised services for rare diseases should not be separated or be in opposition to current programmes for people with disabilities.

DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN BULGARIA

National plan/strategy for rare diseases and related actions

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013).

The Plan officially ended on 31 December 31. Before that, the Ministry of Health had established a working group to prepare a draft for a Second National Plan. The Plan is expected to work closely with the National Rare Disease Registry and the centres of expertise for rare diseases, both of which are supposed to be officialised by the end of 2014. However, no schedule for the adoption and the implementation of the Second Plan was available by the end of 2013.

Centres of expertise

Significant progress was achieved in 2013 regarding the centres of expertise for rare diseases in Bulgaria. The National Assembly voted amendments in the Health Act (Article 144a), requiring the Minister of Health to adopt a regulation, which will establish a National Registry for Rare Diseases, as well as will determine the criteria for designation of centres of expertise for rare diseases. The Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation. The draft regulation also envisages the establishment of a permanent National Rare Diseases Council to the Ministry of Health, as well as an official list of rare diseases. The draft was discussed at several meetings, including the National Conference for Rare Diseases in September 2013. The final draft was submitted to the Ministry of Health early in 2014. This legislation is expected to be approved by the Ministry of Health and to come into force by the end of 2014.

Since September 2013, RareDis and ICRDOD were merged into the Institute for Rare Diseases (IRD), together with the newly-established Centre for Health Technology Assessment and Analyses (CAHTA).

Registries

The idea to implement a National Registry for Rare Diseases re-emerged in 2013. This was motivated by the upcoming implementation of the centres of expertise for rare diseases in the country. Initial plans suggest that the Registry will collect data from these centres and prepare annual reports on rare disease epidemiology. Thus, the Registry will contain only data for rare diseases, for which there are officially designated centres of expertise. However, by the end of 2013 it is not yet decided which institution will coordinate and manage the Registry.

In 2013 ICRDOD established two new registries – for primary myelofibrosis and neuroendocrine tumours.

Sources of information on rare diseases and national help lines

Official information centre for rare diseases

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria¹⁷. The report contains 4 sections: orphan medicinal product designation and marketing authorisation; 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 medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the

¹⁷ Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: http://raredis.org/pub/OD_Report_2013_EN.pdf

drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

Training and education initiatives

Bulgarian rare diseases stakeholders are active in promoting EU rare policy at local and regional level. The country hosted the First Rare Diseases Summer School for Health Authorities and Legislators¹⁸, an event designed to raise awareness of rare diseases among Eastern European health authorities and legislators. The event was successfully organised again in 2012 and 2013 in Greece and Turkey respectively. This initiative is a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations “Genetics” (Russia) and the Italian National Centre for Rare Diseases (CNMR). School participants come from a wide range of public fields – legislative bodies and health authorities, medical institutions, academia. The week-long event covers a variety of topics.

National rare disease events in 2013

Rare Disease Day was marked on 28 February 2013 with events organised by the National Alliance of People with Rare Diseases¹⁹. A series of information, education and charity events took place with a balloon launch in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled “Communication and Support to Patients, Based on Modern Technologies” was held in April in Sofia. Outside of Sofia, a series of rare diseases events were organised in the towns of Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

The 4th Annual Conference on Rare Diseases and Orphan Drugs was organised on 13-14 September 2013 in Plovdiv²⁰. The First National Conference on Rare Diseases for Medical Students was held in parallel, bringing together more than 130 students from medical universities across Bulgaria and neighbouring countries.

Hosted rare disease events in 2013

The Bulgarian Association for Promotion of Education and Science launched and organised in 2005, 2006, 2008 and 2009, the annual “Eastern European Conference on Rare Diseases and Orphan Drugs”. In 2010 for the very first time the event was hosted and co-organised outside Bulgaria, in Saint Petersburg, Russia, in conjunction with the first All-Russian Conference for Rare Diseases and Rarely Used Medical Technologies. It has proved to be an efficient strategy to foster rare diseases progress in Eastern Europe. In 2011, the sixth edition²¹ of this initiative was held and co-organised in Istanbul, Turkey. BAPES acted as a co-organiser of the International Conference on Rare Diseases (ICORD) in 2013, an event that was held on October 31 – November 2 in St. Petersburg, Russia. The Bulgarian National Alliance of People with Rare Diseases initiated and organised a Balkan patient meeting on 24 March 2012 in Sofia and again on 20-21 April 2013. Leading rare diseases experts and patients from Balkan countries took part in this event.

Orphan medicinal products

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria²². The report contains information on important orphan medicinal products activities and explained how they are set up in Bulgaria in 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; and conclusions.

Orphan medicinal product committee

Orphan medicinal products are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. In order to optimise these procedures, in 2011 the two commissions were merged into a single one under the Ministry of Health. Subsequently, the Parliament adopted in 2012 new legislation, by which a National Council for Pricing and Reimbursement of Medicinal Products replaced the Commission at the beginning of 2013. The new body has a status of a State agency and is responsible for both pricing and reimbursement of all medicinal products. Medicinal products’ safety is monitored by the Bulgarian Drugs Agency.

¹⁸ http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf

¹⁹ <http://rare-bg.com/>

²⁰ www.conf2013.raredis.org

²² *Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:* http://raredis.org/pub/OD_Report_2013_EN.pdf

²² *Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:* http://raredis.org/pub/OD_Report_2013_EN.pdf

Other initiatives to improve access to orphan medicinal products

The Centre for Health Technology Assessment and Analyses (CAHTA) officially started activities in September 2013. CAHTA currently operates as an independent unit within the Institute of Rare Diseases in Plovdiv, Bulgaria.

The idea behind the establishment of CAHTA is to complement the current activities of the Institute by covering the increasingly dynamic field of health technology assessment (HTA). Introducing and applying the HTA concept in Bulgaria will allow for more transparency, objectivity and efficiency in the health system. HTA is greatly important in the field of rare diseases and orphan drugs. The extended life expectancy and improved quality of life for patients with rare diseases are the most important outcomes of all rare disease policies. These two directly depend on the timely access to advanced diagnostic and therapeutic health technologies. Proper and reliable assessment of innovative health technologies is not only important for rare diseases – it is crucial for the overall effectiveness of the entire health care system in Bulgaria.

In October 2013 CAHTA co-organised a public lecture and discussion on HTA prospects for Bulgaria at the Medical University of Plovdiv. Professor Ken Stein (University of Exeter Medical School, UK), Dr Edmund Jessop (National Health System England, UK) and Dr. Domenica Taruscio (Istituto Superiore di Sanità, Italy) were guest speakers and moderators. The discussion was followed by a training workshop on HTA on 5 October for all interested stakeholders.

LIST OF CONTRIBUTIONS²³

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²³ The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

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²⁴ All websites and documents were last accessed in May 2014.