A COMPREHENSIVE ANALYSIS

OF ACCESS TO ORPHAN DRUGS IN BULGARIA, BUDGET IMPACT OF MEDICINAL THERAPIES FOR RARE DISEASES AND GOOD PRACTICES FOR RARE DISEASE PATIENT ACCESS TO ORPHAN DRUGS IN THE EU

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A COMPREHENSIVE ANALYSIS OF ACCESS TO ORPHAN DRUGS IN BULGARIA, BUDGET IMPACT OF MEDICINAL THERAPIES FOR RARE DISEASES AND GOOD PRACTICES FOR RARE DISEASE PATIENT ACCESS TO ORPHAN DRUGS IN THE EU

STUDY TOPIC: A comprehensive analysis of access to orphan drugs in Bulgaria, budget impact of medicinal therapies for rare diseases and good practices for rare disease patient access to orphan drugs in the EU

STUDY SUBJECT: medicinal products:

a. with an European Community marketing authorization issued by the European Medicines Agency (EMA) under a centralized procedure until the end of 2013;
b. with an orphan designation under Regulation (EC) 141/2000 or with an exclusive indication for prevention, diagnosis and treatment of rare diseases; without indications for diseases coded C00-D48 under the International Classification of Diseases – tenth revision (ICD-10) of the World Health Organization (WHO).

STUDY COMPONENTS:

a. A comprehensive analysis of access to orphan drugs in Bulgaria

i. a critical review of access to orphan drugs in Bulgaria

ii. delay in access to orphan drugs in Bulgaria

b. Budget impact and socio-economic burden of rare diseases in Bulgaria

i. expenditure for rare disease medicinal therapies in Bulgaria

ii. socio-economic burden and health-related quality of life of rare disease patients in Bulgaria

c. Good practices for rare disease patient access to orphan drugs

i. a critical review of good practices in the EU regarding rare disease patient access to orphan drugs

ii. recommendations on improving rare disease patient access to orphan drugs in Bulgaria

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ABBREVIATIONS

AIFA – Agenzia Italiana del Farmaco

AOTM – Agencja Oceny Technologii Medycznych

BIA – Budget Impact Analysis

EC – European Commission

EMA – European Medicines Agency

EU – European Union

EUNetHTA – European Network for Health Technology Assessment

HTA – Health Technology Assessment

HTAi – Health Technology Assessment International

ICD-10 – International Classification of Diseases, 10th revision

ICER – Incremental Cost-Effectiveness Ratio

INAHTA – International Network of Agencies for Health Technology Assessment

INAMI – Institut National d'Assurance Maladie-Invalidité

ISPOR – International Society for Pharmacology and Outcomes Research

MoH – Ministry of Health

NHIF – National Health Insurance Fund

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

PDL – Positive Drug List

WHO – World Health Organization

QALY – Quality-Adjusted Life Year

CHAPTER 1

INTRODUCTION

1.1. Rare Diseases

Rare diseases pose a threat to citizens of the European Union (EU) in so far as they are life-threatening or chronically debilitating conditions with low prevalence and high degree of complexity. A disease is considered rare when it affects not more than 5 in 10 000 people in EU. Though rare, these diseases have numerous types which affect millions of people. It is estimated that 5000 to 8000 different rare diseases affect or will affect between 29 and 32 million people in EU (close to 400 thousand in Bulgaria). The majority of these patients suffer from even more rare conditions that affect one in 100 000 people or less, making them particularly isolated and vulnerable.[1-11]

Of primary importance to rare disease patients are the principles and values of universality, access to quality healthcare, equity and solidarity. The specific features of these diseases – limited number of patients and limited knowledge and expertise – shape them into an extremely high value-added area at both European and national levels. Broad collaboration of Member States and domestic stakeholders is a guarantee that the scarce knowledge, as well as constrained resources are used in the most efficient way possible to combat effectively rare diseases across EU. Rare diseases require a global approach to prevent considerable rates of morbidity or premature mortality (which is avoidable), and to improve quality of life as well as socio-economic potential of individuals affected and their families.[2-5,7,9-10]

European Commission (EC) and Bulgarian health authorities have undertaken a number of concrete steps to address rare disease-related issues. The White Paper 'Together for Health: A Strategic Approach for EU 2008 – 2013' of 23 October 2007 on EU health strategy, identified rare diseases as a public health priority action area. With a view of improving coordination and coherence of national, regional and local initiatives intended to tackle rare disease issues, and encourage cooperation among research and development centres, the respective national actions in the field of rare diseases are

framed in plans and strategies for rare diseases. These policies focus on shaping an integrated approach to current and future activities in this field, aiming to improve access and equality in prevention, diagnosis and treatment of rare disease patients throughout EU, and Bulgaria, in particular.[3,5]

1.2. Orphan drugs

An orphan drug is a medicinal product that is (1) 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 EU 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 EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment; and (2) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.[2]

These medicines are named ‘orphans’ because under normal market circumstance the pharmaceutical industry is rather uninterested to develop and bring to the market products intended solely for a small number of patients suffering from a very rare disorder. A Regulation on orphan medicinal products (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs) has been proposed in order to establish criteria for designation of orphan drugs in EU and set incentives (e.g. exclusive marketing rights for a period of 10 years, protocol assistance, access to centralized procedure to acquire Community marketing authorization) to foster research, development and placing on the market of medicinal products for treatment, prevention or diagnosis of rare diseases. EU policy in the field of orphan drugs has been a success story. Nonetheless, Member States have not yet ensured full access to each authorised orphan medicinal product.[2-5]

1.3. Specific public health issues of rare diseases and orphan drugs

According to Orphanet data, out of the myriad of known and clinically identified rare disease, only a negligible portion is coded in the International Classification of Diseases, 10th revision (ICD-10). This constitutes a serious obstacle which prevents rare

disease-related issues from becoming visible and identifiable by the health system and society as a whole.

Absence of health policies targeted to rare diseases, and insufficiency of expertise, result in delayed diagnosis and hindered access to healthcare. On its part, this leads to additional physical, psychological and mental impairments of patients, to inadequate or even damaging treatments as well as to loss of trust in the health system, despite the fact that some rare diseases allow for leading a normal life, should they be diagnosed on time and treated appropriately.

Wrong or absent diagnosis is the major hindrance to improving quality of life of the numerous rare disease patients.[3-5,10-12] Accessibility and quality of healthcare services for diagnosis, treatment and rehabilitation of such patients differ substantially in the different Member States. This is why an increasing number of countries undertake successful actions to address the issues stemming from disease rarity.[3-5,10-23]

Rare diseases and orphan drugs are the topic of ever more extensive discussions on contemporary public healthcare. Medical science development and new health technology uptake contribute significantly to improving population health status. However, this bears a price – a constant increase in healthcare costs and accumulation of a substantial financial deficit. A number of objective public health factors, such as aging population and rising prevalence of chronic and malignant diseases, bring health authorities to the dilemma of what reforms to initiate in order to limit healthcare costs without obstructing access to adequate and quality healthcare. While European measures fostering development of new rare disease therapies prove to be an undoubted success, access to such therapies remains a problem at national level. Rare disease patients need an extended life expectancy and improved quality of life. An adequate access to approved innovative therapies will support meeting patients' expectations.[24-28]

In EU, orphan drugs are subject to a marketing authorization issued under a centralized procedure, as prescribed by Regulation (EC) 726/2004. However, Member States regulate independently the access to such medications. The process can be long and sometimes complicated. Data of a 2012 survey indicate that the time span between acquiring an EMA marketing authorization for an orphan drug and its inclusion in Bulgaria's Positive Drug List (PDL) annexes averages 43 ± 29.1 months. This is a major constraint to a timely and adequate treatment of rare disease patients. It is worth point

out, however, that this big access delay has complex causes. Some marketing authorization holders do not register the product in Bulgaria, mostly because of the country's small market size. Public healthcare funds and availability of a clear and transparent framework for assessment of these medicinal products could be listed among the other possible causes affecting orphan drug access.[29-35]

1.4. Rare disease health technology assessment and budget impact analysis

The concept of health technology assessment (HTA) has been in existence for some decades now, but it is the economic crisis and fiscal pressure that have evoked health authorities' interest in this discipline. HTA plays an increasingly active role in informed decision-making on access to innovative health technologies. HTA outcomes enable health authorities to balance clinical, economic, social, ethical and other considerations when public funds on healthcare are to be spent.

Traditional HTA criteria applied to assessment of innovative health technologies for rare diseases bring about some serious issues. Orphan drugs are life-supporting therapies and usually are the first efficacious therapeutic approaches to handling the diseases. Typically, initial assessment relies on surrogate indicators and a limited set of scientific evidence but the high price of these medications renders them cost-ineffective. Accounting for several socio-ethical factors makes the final decision very difficult and to a major extent, contravertial.[26-47]

HTA supports informed decision-making on reimbursement while accounting for both clinical and economic evidence. In view of objective fiscal constraints, health authorities require also information about the impact of any new technology on the limited budget available. If a decision on access to a health technology is to be taken on the basis of HTA, it is the budget impact analysis (BIA) that will provide the quantity of resources required to implement such a decision. The International Society for Pharmacology and Outcomes Research (ISPOR) recommends such analyses to take into account the respective health system specifics, possible access constraints, expected market penetration, and impact on available and accessible health technologies.[36-37,48-50]

One of the reasons for a restricted and delayed access to rare disease medicinal therapies refers to the concerns about expenditure for these medicinal products (in total

and per patient) at national level. Along with these concerns, empirical evidence available to perform a budget impact estimation of these therapies in Europe is insufficient. The first such analysis for rare diseases was conducted in 2004 and established that the share of orphan drug expenditure was 0.7-1.0% of the total public expenditure for medicinal products. An increase to 6-8% by 2010 was also forecast. Latest studies indicate contradictory results – some claim a slow but lasting increase in the share of orphan drug expenditure by 2016, maintaining a level of 4-6% onwards. Others report an average annual expenditure growth of 13%-28%. Undoubtedly, all these analyses contribute to a better understanding of expenditure developments and volumes for rare disease therapies in EU. Nonetheless, not many analyses are based on actual data, and even if they are, the period covered is usually very short.[51-54]

Over the last decade, rare disease issues have gained an increasing visibility in Bulgaria. The country is the first in Eastern Europe to adopt a national programme for rare diseases. Recent years have marked also considerable changes regarding access to medicinal therapies for rare diseases. The last change introduced at the end of 2010 refers to rare disease medicines being included in the mandatory health insurance coverage. Since March 2011, the National Health Insurance Fund (NHIF) has been reimbursing medicinal therapies for rare diseases included in the list for outpatient care under MoH Regulation 38. Prior to this, it was the Ministry of Health that paid for these medicines, with the budget being allocated on the grounds of previous year spending. These therapies were purchased under annual centralized tenders, making the health system operate within a fixed quantity of medicines. Transfer of rare disease medicinal therapies coverage to NHIF was justified also by the need of securing equal access to healthcare of rare disease patients, just like any other patient.[10,15-17,22-23,30,38]

CHAPTER 2

OBJECTIVES

The comprehensive analysis contains three study components which are the following:

A. A comprehensive analysis of access to orphan drugs in Bulgaria

i. a critical review of access to orphan drugs in Bulgaria

ii. delay in access to orphan drugs in Bulgaria

B. Budget impact and socio-economic burden of rare diseases in Bulgaria

i. expenditure for rare disease medicinal therapies in Bulgaria

ii. socio-economic burden and health-related quality of life of rare disease patients in Bulgaria

C. Good practices for rare disease patient access to orphan drugs

i. a critical review of good practices in the EU regarding rare disease patient access to orphan drugs

ii. recommendations on improving rare disease patient access to orphan drugs in Bulgaria

2.1 Component A aims to review critically access to orphan drugs in Bulgaria and analyse delay in such access. The study reports on orphan drugs available in Europe and the portion accessible nationally. Also, the study looks into topical methodological challenges in HTA application to innovative medications for rare diseases. Addressing adequately such challenges is a key factor to securing treatment access of the end-user – the patient. The analysis focuses on the role and importance of two leading HTA criteria – clinical effectiveness and cost-effectiveness of the relevant health technology. The most frequent practical issues in identifying and assessing clinical effectiveness and cost-effectiveness of innovative medicinal therapies for rare diseases are summarized. Good practices to overcome these issues are also presented.

2.2 Component B aims to assess impact of outpatient medicinal therapies for rare diseases on NHIF total budget for medications in the years 2011 – 2014, and identify key factors pertaining to the magnitude and dynamic of this indicator. The study outlines the importance of the availability and accessibility of rare disease medicinal therapies to the average expenditure and number of patients treated. Tools to manage budget impact uncertainty associated with rare disease medicinal therapies, proven to be applicable and effective in other countries are also reviewed.

2.3 Component C aims to identify, analyse and present good practices for rare disease patient access to orphan drugs. Representatives of access-related bodies in EU Member States are surveyed. Relevant scientific literature and regulations are reviewed. The overall framework of product registration, assessment and reimbursement, principal actors, actors' objectives, tasks and powers, and public funding modalities for rare disease therapies is analysed. Special emphasis is given to the so-called risk-sharing agreements – reimbursement mechanisms, negotiated and adopted jointly by health authorities and industry. The analysis compares these qualitative indicators and on the ground of the outcomes draws up concrete recommendations on improving rare disease patient access to orphan drugs in Bulgaria.

CHAPTER 3

MATERIAL AND METHODS

3.1. Study design – Component A

3.1.1. Quantitative indicators for availability and access to orphan drugs

Subject of the study were medicinal products designated as orphan, in accordance to Regulation 141/2000, and having a marketing authorization issued at the time of the study (July 2014).[2,29] Approved orphan drugs without an official 'orphan' designation or drugs with a repealed designation were excluded. EMA registers served as a source of the total number of orphan drugs available in EU, namely: register of designated orphan medicinal products and register of approved medicinal products.[55-56] The outcomes were analysed in light of the relevant Bulgarian legislation on registration, pricing and reimbursement of medicinal products in order to obtain the final list of orphan drugs accessible in Bulgaria.[57-63] For the purposes of the study, the term 'access' was defined as a possibility for a timely and reimbursed treatment. In this context, officially approved and registered orphan drugs in EU were considered 'available' but only when included in the public healthcare system by means of an effective reimbursement scheme and used routinely in the treatment of rare disease patients, they would become 'available'.[30]

3.1.2. Challenges in orphan drug assessment and reimbursement decision-making

Component A was supplemented by an review of peer reviewed scientific publications contained in MEDLINE, National Health Service (NHS) Economic Evaluation Database и Cochrane Database of Systematic Reviews databases and surveyed between 15 May and 15 July 2014. Information retrieval was not confined by time of publishing and type of article. Search English words and word combinations used

were the following: rare diseases; orphan drugs; medicinal therapies; innovative therapies; health technology assessment; effectiveness; clinical effectiveness; cost-effectiveness; pricing; reimbursement, decision-making; access; budget; regulations. Bibliography of major publications relevant to the review topic was also considered.

3.2. Study design – Component B

3.2.1 List of rare diseases in Bulgaria

The European definition of a rare disease is officially adopted in Bulgaria, namely, a disease affecting not more than 5 in 10 000 people in EU.[57] However, as of today, there is no formal Bulgarian list of diseases considered by health authorities as rare, nor are official epidemiological data available to establish whether a disease falls into this category or not.[64-65]

Table 1. Criteria for excluding a disease from study scope

	Exclusion criteria
1	Infectious and parasitic diseases (ICD-10, code A00 to B99)
2	Neoplasms (ICD-10, code C00 to D48)
3	Mental and behavioural disorders (ICD-10 code F00 to F99)
4	Factors influencing heath status and contact with heath services (ICD-10 code Z00 to Z99)
5	High prevalence / absence of ORPHA code

The first criterion for inclusion was presence in the list of diseases for which the home treatment with medicines, medical devices and diet food for special medical purposes was paid in full or in part by NHIF.[62] A list containing ICD-10 codes of all diseases meeting the criterion was drawn up. All infectious and parasitic diseases (ICD-10 code A00 to B99), neoplasms (ICD-10 code C00 to D48), mental and behavioural disorders (ICD-10 code F00 to F99), factors influencing health status and contact with health services (ICD-10 code Z00 to Z99) were excluded (Tables 1 and 2).

Table 2. List of diseases excluded from study scope

ICD-10 code	Disease	Exclusion criterion
A38	Scarlet fever	1
B18	Chronic viral hepatitis	1
B67.0;B67.1;B67.3B 67.5;B67.6	Ehinococcus granulosus	1
C50	Malignant neoplasm of breast	2
C54.1	Malignant neoplasm of endometrium	2
C61	Malignant neoplasm of prostate	2
C64	Malignant neoplasm of kidney, except renal pelvis	2
D50.0	Iron deficiency anaemia secondary to blood loss (chronic)	5
E03	Hypothyroidism, unspecified	5
E04.0	Nontoxic diffuse goiter	5
E05.0,E05.1, E05.2, E05.3,E05.4	Thyrotoxicosis	5
E06	Thyroiditis	5
E10.2,E10.3,E10.4, E10.5,E10.9	Diabetes mellitus	5
E11	Diabetes mellitus with hyperosmolarity	5
E22.1	Hypersprolactinemia	5
E89.2	Postprocedural hypoparathyroidism	5
E89.4	Postprocedural ovarian failure	5
F20	Schizophrenia	3
F30-F33	Mood disorders	3
G20	Parkinson disease	5
G30	Alzheimer disease	5
G35	Multiple sclerosis	5
G40.6	Grand mal seizures (with or without small seizures (petit mal), unspecified	5
G40.7	Petit mal seizures, without grand mal seizures, unspecified	5
G54.0,G54.1,G54.2, G54.3,G54.4, G54.5,G54.6	Nerve root and plexus disorders	5
G63.2	Diabetic polyneuropathy	5
G80	Cerebral palsy in children	5
H16.0,H16.1,H16.2, H16.3,H16.4	Katitis	5
H20.0	Acute and subacute iridocyclitis	5
H36.0	Diabetic retinopathy	5
H40	Glaucoma	5
H66.0	Acute suppurative otitis media	5
I10-I13	Hypertensive diseases	5
I20	Angina pectoris	5
I25.5	Ischemic cardiomyopathy	5
I26.0	Pulmonary embolism with acute cor pulmonale	5
I44.2	Atrioventricular block, complete	5
I45.6	Pre-excitation syndrome	5

I47.1	Supraventricular tachycardia	5
I48	Atrial fibrillation and flutter	5
I49.5	Sick sinus syndrome	5
I50.0,I50.1	Heart failure	5
I69	Sequelae of cerebrovascular disease	5
I73.1	Thromboangiitis obliterans (Buerger disease)	5
I80.0,I80.1,I80.2	Phlebitis and thrombophlebitis	5
J03	Acute tonsillitis	5
J15,J16	Pneumonia	5
J40	Bronchitis, not specified as acute or chronic	5
J42	Chronic bronchitis, unspecified	5
J44.8	Other chronic obstructive lung disease	5
J45.0,J45.1	Asthma	5
K12.0	Recurrent oral aphthae	5
K12.1	Other forms of stomatitis	5
K20	Esophagitis	5
K25.7	Chronic gastric ulcer without hemorrhage or perforation	5
K26	Duodenal ulcer	5
K51.2	Ulcerative (chronic) proctitis	5
K51.3	Ulcerative (chronic) rectosigmoiditis	5
K52.2	Allergic and dietetic gastroenteritis and colitis (allergy to cow milk protein)	5
K74	Fibrosis and cirrhosis of liver	5
K90.0	Celiac disease	5
L40	Psoriasis	5
M05	Seropositive rheumatoid arthritis	5
M07.1,M07.2,M07.3	Psoriatic and enteropathic arthropathy	5
M32	Disseminated lupus erythematosus	5
M45	Ankylosing spondylitis	5
M80	Osteoporosis with current pathological fracture	5
M81	Osteoporosis without current pathological fracture	5
N10	Acute tubulo-interstitial nephritis	5
N11	Chronic tubulo-interstitial nephritis	5
N18	Chronic kidney disease	5
N31	Neuromuscular dysfunction bladder, not elsewhere classified	5
N40	Hyperplasia of prostate	5
N80	Endometriosis	5
Q21.8	Other congenital malformations of cardiac septa	5
Z43.2	Encounter for attention to ileostomy	4
Z43.3	Encounter for attention to colostomy	4
Z43.5	Encounter for attention to artificial openings	4
Z43.6	Encounter for attention to other artificial openings of urinary tract	4
Z94	Transplanted organ and tissue status	4

For the purposes of the study, the final rare disease list was complied after checking prevalence rates on Orphanet.[66] Diseases with a prevalence of over 5 in 10 000 people and no Orpha code were excluded (Tables 2 and 3).

Table 3. List of diseases considered as rare according to study scope

ICD-10 code	Disease
D56.1	Beta thalassemia (thalassemia major)
D66, D67,D68.0,D68.2	Coagulation defects
D69.3	Idiopathic thrombocytopenic purpura
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G
D81.2	Severe combined immunodeficiency with low or normal B-cell numbers
D83.8	Other common variable immunodeficiency
D84.1	Defects in the complement system (C1 esterase inhibitor deficiency)
E22.0	Acromegaly and pituitary gigantism
E22.8	Other hyperfunction of pituitary gland
E23.0	Hypopituitarism
E23.2	Diabetes insipidus
E24.0	Cushing syndrome of pituitary origin
E27.1	Primary adrenocortical insufficiency
E55.0	Rickets, active
E70.0	Classical phenylketonuria
E72.2	Disorders of urea cycle metabolism
E74.0	Glycogen storage disease
E75.2	Gaucher disease, Fabry disease, Niemann-Pick disease
E76	Mucopolysaccharidosis
E83.0	Wilson-Konovalov disease
E83.3	Disorders of phosphorus metabolism
E84	Cystic fibrosis
E85.1	Neuropathic heredofamilial amyloidosis
G70.0	Myastenia gravis
G71.0,G71.1,G71.2,G71.9	Primary muscular disorders
I27.0	Primary pulmonary hypertension
K50.0,K50.1	Crohn disease
M08	Juvenile arthritis
M30.0	Polyarteritis nodosa
M31.3	Wegener granulomatosis
M33	Dermatopolymyositis
M34	Systemic sclerosis
P27.1	Bronchopulmonary dysplasia originating in the perinatal period
Q87.1	Prader-Willi syndrome
Q96	Turner syndrome

3.2.2 Budget impact of medicinal therapies for rare diseases

Budget impact of rare disease therapies was identified from the perspective of NHIF (i.e. only outpatient medicinal therapy costs paid by NHIF were included). The study looked only into official data (2011-2014) about NHIF expenditure for medicinal therapies. Analysed were also NHIF quarterly reports regarding total reimbursement amount and number of health insured persons, by ICD-10 code.[67]

Data were described by means of descriptive statistics (average total expenditure per rare disease, average expenditure per patient and average total number of reimbursed health insured persons) while average growth rates were calculated to analyse the dynamics of the rare disease budget impact, using chain method (each previous period serves as a basis for the period analysed).[68] Inflation was not accounted for since the study time range was relatively short. All data reflected actual NHIF expenditure in local currency.

3.3. Study design – Component C

3.3.1. Survey of good practices for rare disease patient access to orphan drugs

Good practices for access to orphan drugs were identified by means of questionnaires filled in individually and directly. The questionnaire (Attachment 1) contained 58 open and closed questions, to be answered online and in English. The survey had an international coverage.

Questions were grouped in sections encompassing all important stages of the process of providing adequate and effective access to rare disease medicinal therapies – registration, alternative mechanisms for access to non-registered medicinal products, alternative mechanisms for access to registered non-reimbursed medicinal products, management of medicinal therapy costs for rare diseases. The questionnaire's initial page presented an overview of the study, its purpose, objectives and methodology. Respondents were given the opportunity to ask questions before filling in the questionnaire online.

Questions were selected with particular regard to funding sources for each activity pertinent to access to rare disease medicinal therapies, institutions in charge,

institutions' powers and responsibilities. Respondents were asked to provide a reference to the information filled in, preferably a scientific article or regulation.

Respondents were selected on the basis of the following criteria: (1) a representative of an institution having a bearing on registration, pricing, assessment, decision-making on reimbursement and/or funding of medicinal therapies for rare diseases; (2) documented experience and expertise such as scientific publications in international peer reviewed journals with an impact factor, experience in European projects and working groups in the field of rare diseases and orphan drugs. Prior to survey launch, each respondent was asked to confirm participation. Invitations to survey respondents were sent on 1 July 2014 and contained links to the questionnaire. They were given a month and half to fill it in. Responses were entered anonymously and were recorded on a protected server. Due to the small sample size and the qualitative nature of the data, results were not subjected to statistical processing.

3.3.2. A critical review of good practices for access to orphan drugs in the EU and, in particular, implementation of risk-sharing agreements

Component B of the Study was supplemented by a critical review and analysis of peer reviewed scientific publications in MEDLINE, National Health Service (NHS) Economic Evaluation Database и Cochrane Database of Systematic Reviews databases, surveyed from 15 July to 15 September 2014. Retrieval was not confined to time of publishing and type of article. For the purposes of the review, the following definition of risk-sharing agreement was used – a contract between the payer and the manufacturer where the price, rate and nature of reimbursement are linked to future outcomes regarding patient's life expectancy and quality of life. Search English words and word combinations used were the following: rare diseases; orphan drugs; medicinal therapies; drug policy; drug regulations; registration; pricing; assessment; reimbursement; medication budget; overspending; uncertainty; financial risk; risk management; risk-sharing; health outcomes; performance-based guarantees; evidence-based guarantees. Bibliography of major publications relevant to the review topic was also considered.

CHAPTER 4

RESULTS AND DISCUSSION

4.1. Component A

4.1.1. Availability of orphan drugs

EC grants a marketing authorization for orphan drugs under a centralized procedure following an EMA recommendation, as prescribed by Regulation 726/2004 of the European Parliament and of the Council of 31 March 2004. The Regulation is applicable to all countries of the European Union. By definition, these marketing authorizations are '*in the interest of public health*' and are based on '*objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations*'.[29] The mechanism itself is one of the incentives that European authorities provide to the pharmaceutical industry for research and development of rare disease medicinal products. These include:[2]

- accelerated assessment procedure for medicinal products of particular importance to public health and more specifically, representing an innovation from a therapeutic point of view;
- EMA commitment to draw up and submit opinions on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, in compliance with the relevant European requirements;
- reduction of fees, fee payment deference, assuming responsibility for deals, and provision of administrative assistance. As per Article 7 of Regulation 141/2000, every year the Community allocates a contribution to EMA to be used exclusively for waiving in part or in full all fees payable under Community rules adopted pursuant to the Regulation;
- market exclusivity – as per Article 8 of Regulation 141/2000, the Community and the Member States are to refrain from accepting another application for a

marketing authorisation, to grant a marketing authorisation or satisfy an application to extend an existing marketing authorisation, for the same therapeutic indication (of the registered orphan drug) for a period of 10 years;

- medicinal products designated as orphan are eligible for incentives made available by the Community and by the Member States to support research, development and marketing of orphan medicinal products and, in particular, aid for research provided to small- and medium-sized enterprises under framework programmes for research and technological development.

This entire incentive package comes in response to the fact that the majority of rare diseases are so rare that development and marketing costs of a medicinal product for diagnosis, prevention or treatment cannot be covered by sales expected. The pharmaceutical industry is rather hesitant when it comes to investing in such medicinal products under normal market conditions.[26,44,69-70]

As of July 2014, 72 medicinal products have an active orphan designation and a marketing authorization granted by EC (Table 4).

Table 4. Medicinal products with a valid orphan designation and an EU marketing authorization issued, as of August 2014

Trade name	Active ingredient	ATC code	Marketing authorization date
Adcetris	brentuximab vedotin	L01XC12	25/10/2012
Adempas	riociguat	C02KX05	27/03/2014
Arzerra	ofatumumab	L01XC10	19/04/2010
Atriance	nelarabine	L01BB07	22/08/2007
Bosulif	bosutinib	L01XE14	27/03/2013
Bronchitol	mannitol	R05CB16	13/04/2012
Cayston	aztreonam lysine	J01DF01	21/09/2009
Ceplene	histamine dihydrochloride	L03AX14	07/10/2008
Cholic Acid FGK	cholic acid	A05AA03	04/04/2014
Cometriq	cabozantinib	L01XE	21/03/2014
Cystadane	betaine anhydrous	A16AA06	15/02/2007
Dacogen	decitabine	L01BC08	20/09/2012
Defitelio	defibrotide	B01AX01	18/10/2013
Deltyba	delamanid	J04AK06	28/04/2014
Diacomit	stiripentol	N03AX17	04/01/2007
Elaprase	idursulfase	A16AB09	08/01/2007

Esbriet	pirfenidone	L04AX05	28/02/2011
Evoltra	clofarabine	L01BB06	29/05/2006
Exjade	deferasirox	V03AC03	28/08/2006
Firazyr	icatibant	C01EB19	11/07/2008
Firdapse	amifampridine	N07XX05	23/12/2009
Gazyvaro	obinutuzumab	L01XC15	23/07/2014
Gliolan	5-aminolevulinic acid hydrochloride	L01XD04	07/09/2007
Glybera	alipogene tiparvovec	C10 AX10	25/10/2012
Granupas	para-aminosalicylic acid	J04AA01	07/04/2014
Iclusig	ponatinib	L01XE24	01/07/2013
Imnovid	pomalidomide	L04AX06	05/08/2013
Increlex	mecasermin	H01AC03	03/08/2007
Inovelon	rufinamide	N03AF03	16/01/2007
Jakavi	ruxolitinib	L01XE18	23/08/2012
Kalydeco	ivacaftor	R07AX02	23/07/2012
Kuvan	sapropterin dihydrochloride	A16AX07	02/12/2008
Mepact	mifamurtide	L3AX15	06/03/2009
Mozobil	plerixafor	L03AX16	31/07/2009
Myozyme	alglucosidase alfa	A16AB07	29/03/2006
Naglazyme	galsulfase	A16AB	24/01/2006
Nexavar	sorafenib	L01XE05	19/07/2006
NexoBrid	concentrate of proteolytic enzymes	D03BA03	18/12/2012
Nplate	romiplostim	B02BX04	04/02/2009
Opsumit	macitentan	C02KX04	20/12/2013
Orfadin	nitisinone	A16AX04	21/02/2005
Orphacol	cholic acid	A05AA03	12/09/2013
Peyona	caffeine citrate	N06BC01	02/07/2009
Plenadren	hydrocortisone	H02AB09	03/11/2011
Prialt	ziconotide	N02BG08	21/02/2005
Procysbi	mercaptamine bitartrate	A16AA04	06/09/2013
Revatio	sildenafil	G04BE03	28/10/2005
Revestive	teduglutide	A16AX08	30/08/2012
Revlimid	lenalidomide	L04AX04	14/06/2007
Rilonacept Regeneron	rilonacept	L04AC08	23/10/2009
Savene	dexrazoxane hydrochloride	V03AF02	28/07/2006
Signifor	pasireotide diaspartate	H01CB05	24/04/2012
Siklos	hydroxycarbamide	L01XX05	29/06/2007
Sirturo	bedaquiline fumarate	J04A	05/03/2014

Soliris	eculizumab	L04AA25	20/06/2007
Sprycel	dasatinib	L01XE06	20/11/2006
Sylvant	siltuximab	-	22/05/2014
Tasigna	nilotinib	L01XE08	19/11/2007
Tepadina	thiotepa	L01AC01	15/03/2010
Thalidomide Celgene	thalidomide	L04AX02	16/04/2008
Tobi Podhaler	tobramycin	J01GB01	20/07/2011
Torisel	temsirolimus	L01XE09	19/11/2007
Vidaza	azacitidine	L01BC07	17/12/2008
Vimizim	recombinant human n-acetylgalactosamine-6-sulfatase	A16AB12	28/04/2014
Volibris	ambrisentan	C02KX02	21/04/2008
Votubia	everolimus	L01XE10	02/09/2011
Vpriv	velaglucerase alfa	A16AB10	26/08/2010
Vyndaqel	tafamidis	N07XX08	16/11/2011
Wilzin	zinc	A16AX05	13/10/2004
Xagrid	anagrelide	L01XX35	16/11/2004
Xaluprine	6-mercaptopurine monohydrate	L01BB02	09/03/2012
Yondelis	trabectedin	L01CX01	17/09/2007

In the last two and half years some new 27 orphan medicines have been approved for marketing, 9 of them – in the first half of 2014 (Table 5, Figure 1). This trend can be considered as a direct outcome of the enhanced support for development of new rare disease therapies provided by EC in the recent years. The International Rare Disease Research Consortium, established in 2011, is expected to foster this upside trend in the coming years. All this confirms that European health authorities regard rare disease patient access to treatment as an issue of high public health and political relevance.[23,26,51,71-75]

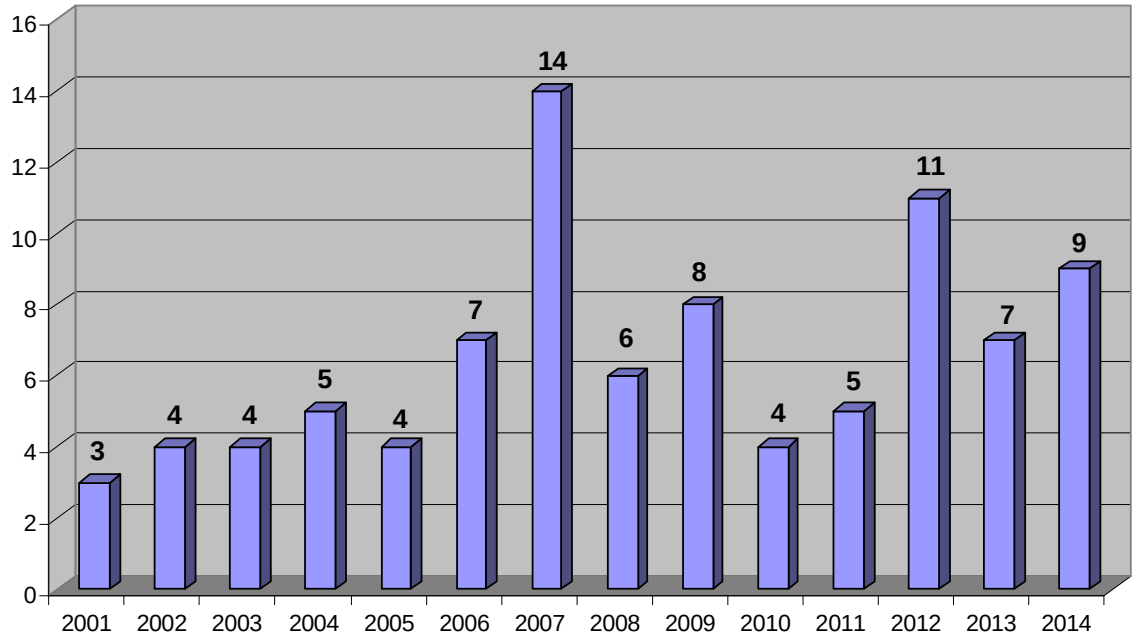

Figure 1. Annual number of orphan drug marketing authorizations issued by EC

The majority of designated medicines are indicated for oncological diseases and this is an ongoing trend (Table 5). Lysosomal storage disease and primary pulmonary hypertension seems to be the industry's next 'most preferred' developmental areas for new medicinal products. It is worth noting that the number of orphan drugs available at European level is dynamic – newly approved products are added while others are removed from the market, namely those with an expired market exclusivity or even earlier, at the discretion of the marketing authorization holder. (Tables 5 and 6).

Table 5. Newly approved orphan medicinal products for the period July 2013 – August 2014

	Trade name	Active substance	Indication	Year of marketing authorization
	Adempas	riociguat	Chronic thromboembolic pulmonary hypertension Pulmonary arterial hypertension	2014
	Cholic Acid FGK	cholic acid	Congenital primary bile acid systhesis defects	2014
	Cometriq	cabozantinib	Medullary thyroid carcinoma	2014

	Defitelio	defibrotide	Veno-occlusive disease	2013
	Deltyba	delamanid	Multi-drug resistant pulmonary tuberculosis	2014
	Gazyvaro	obinutuzumab	Chronic lymphocytic leukaemia	2014
	Granupas	para-aminosalicylic acid	Multi-drug resistance tuberculosis	2014
	Imnovid	pomalidomide	Multiple myeloma	2013
	Opsumit	macitentan	Pulmonary arterial hypertension	2013
	Orphacol	cholic acid	Congenital primary bile acid systhesis defects	2013
	Procysbi	mercaptamine bitartrate	Nephropathic kidney) cystinosis	2013
	Sirturo	bedaquiline fumarate	Multi-drug resistant pulmonary tuberculosis	2014
	Sylvant	siltuximab	Multicentric Castleman's disease	2014
	Vimizim	recombinant human n-acetylgalactosamine-6-sulfatase	Mucopolysaccharidosis type IV A	2014

In any case, the number of these products has been maintained in the vicinity of over 60 in the recent years. Following a period of a relative 'stand-still' in 2010 and 2011, we witnessed, yet again, a growth in marketing authorization approvals for orphan drugs in 2012. In that sense, 2012 could be considered 'the most successful' year although the growth prospects for 2014 might surpass it (Figure 1).

Table 6. Medicinal products with an expired orphan designation (expired 10-year market exclusivity) for the period July 2013 – August 2014

	Trade name	Active ingredient	Indication	Year of marketing authorization
	Litak	cladribine	Hairy cell leukaemia	2004
	Lysodren	mitotane	Advanced adrenocortical carcinoma	2004

	Pedea	ibuprofen	Open ductus arteriosus	2004
	Ventavis	iloprost	Primary pulmonary hypertension	2003

4.1.2. Access to orphan drugs

While at EU level decision-making on issuing an orphan drug marketing authorization is taken by EC under EMA recommendation, it is the national authorities that regulate access to and use of such medications in individual Member States.[26,30,33]

Table 7. Reimbursement status of orphan medicinal products with an EU marketing authorization in Bulgaria, as of August 2014

Trade name	Indication	A1	A2
Arzerra	Chronic lymphocytic leukemia	–	yes
Atriance	Acute T-cell acute lymphoblastic leukaemia; T-cell lymphoblastic lymphoma	–	yes
Cayston	Mucoviscidosis	–	yes
Elaprase	Mucopolysaccharidosis type II	yes	yes
Evoltra	Acute lyphoblastic leukaemia	–	yes
Exjade	Beta thalassaemia major	yes	yes
Jakavi	Myelofibrosis	–	yes
Kuvan	Phenylketonuria; tetrahydrobiopterin deficiency	yes	yes
Mozobil	Collection of hematopoietic steam cells for transplantation in lymphoma or multiple myeloma	–	yes
Myozyme	Pompe disease	yes	yes
Naglazyme	Mucopolysaccharidosis type VI	yes	yes
Nexavar	Hepatocellular carcinoma, advanced renal cell carcinoma	yes	yes
Nplate	Chronic immune thrombocytopenic purpura	–	yes
Revatio	Pulmunary arterial hypertension	yes	yes
Sprycel	Ph+ chronic myeloid leukaemia, Ph+ acute lymphoblastic leukaemia	yes	yes
Tasigna	Ph+ chronic myeoloid leukaemia	yes	yes
Tobi Podhaler	Mucoviscidosis	yes	yes
Torisel	Advanced renal cell carcinoma, mantle cell lymphoma	–	yes
Volibris	Pulmunary arterial hypertension	yes	yes
Vyndaqel	Transthyretin amyloidosis	yes	yes
Xagrid	Essential thrombocythemia	–	yes
Yondelis	Advanced soft tissue sarcoma, ovarian cance	–	yes

Among the key legislative pieces addressing access to orphan drugs in Bulgaria are the Ordinance on the terms, rules and procedures for regulation and registration of medicinal product prices and Regulation 38 on identifying the list of diseases for home treatment with medicines, medical devices and diet food for special medical purposes paid in full or in part by the National Health Insurance Fund (NHIF).[60,62]

Out of the 72 orphan drugs available in EU as of July 2014, only one is included in Annex 1 (Medicinal products intended for treatment of diseases that are paid for under the procedures of the Law on Health Insurance), ten – in Annex 2 (Medicinal products paid for by the budget of medical establishment, pursuant to Article 5 of the Law on Medical Establishments, and by the budget of medical establishments with a state and/or municipal participation, pursuant to Articles 9 and 10 of the Law on Medical Establishments), while eleven are present in both annexes (Table 7 and 8, Figures 2 and 3). For one reason or another, the remaining 50 orphan drugs are not present in the PDL annexes. That is why they cannot be reimbursed with public funds and in fact, remain inaccessible to patients with the respective rare diseases in Bulgaria.

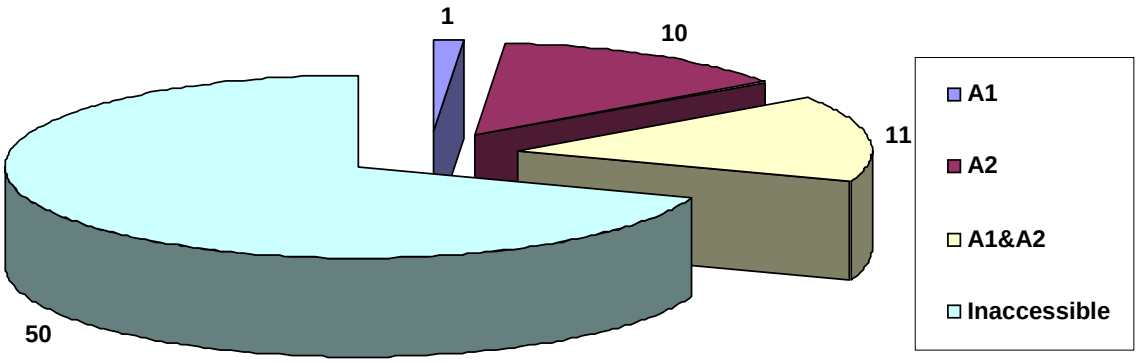

Figure 2. Reimbursement status of orphan medicinal products with an EU marketing authorization in Bulgaria, as of August 2014

In comparison, surveys in other Member States indicate that an average of about 80% of the EU approved orphan drugs are incorporated in the health insurance system. As for the remaining portion, duly regulated and efficient alternative channels for access to orphan drugs are put in place by the majority of Member States. In other words, rare disease patients in these countries enjoy a timely access to all therapies having a registered orphan designation status.[4,30-35,44-46]

Two aspects need to be considered here. On the one hand, over two-thirds of the products remain inaccessible to Bulgarian patients. On the other hand, however, there is a gradual upward trend in access provision observed in the years 2010 – 2014. Access to orphan drugs for rare diseases does not depend solely on the financial capacity of a health system. It is also a consequence of clear, objective and transparent rules put in place for registration, pricing, assessment and reimbursement decision-making.[31-33,37-38]

Table 8. Changes in the reimbursement status of orphan medicinal products and an EU marketing authorization in Bulgaria, as of August 2014

	Trade name	Active ingredient	Indication	Year of marketing authorization
	Arzerra	ofatumumab	Chronic lymphocytic leukemia	2010
	Atriance	nelarabine	Acute T-cell acute lymphoblastic leukaemia; T-cell lymphoblastic lymphoma	2007
	Jakavi	ruxolitinib	Myelofibrosis	2012
	Kuvan	sapropterin dihydrochloride	Phenylketonuria Tetrahydrobiopterin deficiency	2008
	Naglazyme	galsulfase	Mucopolysaccharidosis type VI	2006
	Xagrid	anagrelide	Essential thrombocythemia	2004

Several political measures have been undertaken in this period:

- adopting a National Programme for Rare Diseases (2009 – 2013);
- transferring outpatient medicinal therapies from MoH to the mandatory health insurance coverage;
- amending the regulatory framework on price registration and inclusion of the medicinal products in PDL;
- establishing a National Council on Prices and Reimbursement of Medicinal Products;
- adopting a Regulation on registration of rare diseases and setting up rare disease expert centres and reference networks.

Albeit some do not target directly rare diseases, the above measures are a clear signal about a political will to tackle the issues of rare disease patients in Bulgaria,

including equal and fair access to treatment. Both patients and physicians stand unanimous for the changes and believe that they are a step forward in the right direction. These measures should not be repealed. On the contrary, they should be enhanced via additional measures, including post-marketing surveillance, epidemiological registers and risk-sharing agreements.

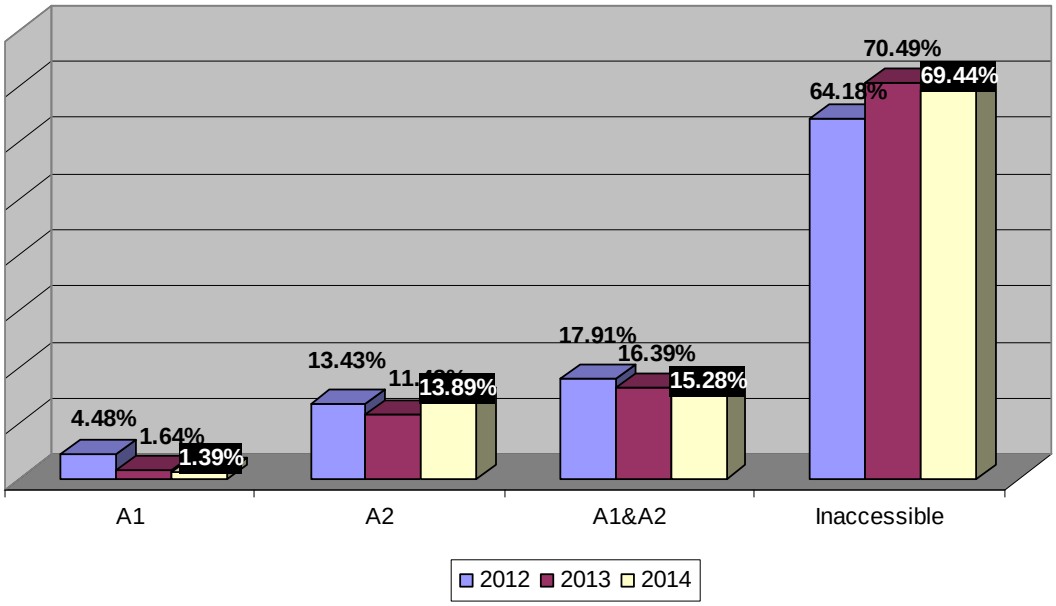

Figure 3. Dynamics of access to orphan drugs in Bulgaria for the period 2012 – 2014

4.1.3. Clinical effectiveness of orphan drugs

Health technology assessment with its methodology, procedures and rules, and the subsequent decision-making regarding reimbursement with public funds, is a key factor affecting access to medicinal therapies for rare diseases. Orphan drugs as well as HTA concept are relatively new notions in public health. This is why, from methodological perspective, there is a set of problematic issues which are essential to acquiring a positive assessment of innovative medicinal therapies for rare diseases and including such therapies in the health insurance coverage.[31-38]

Firstly, there is the question of clinical effectiveness of orphan drugs. Immediately following the time of acquiring a marketing authorization and before securing an effective access to the product, volume and level of evidence regarding clinical effectiveness of such therapies, is often considered unsatisfactory by health authorities. Frequently, the questions of product long-term efficacy, safety and optimal dose are raised. The follow-

up period in clinical trials is relatively short as compared to the natural history of the rare disorder in question. Rare disease clinical studies are hindered additionally by the small number of study subjects. All these specific features are important for the objective assessment of clinical effectiveness. At EU level, EMA substantiates drug approval decisions on quality, safety and efficacy of medicinal products. At national level, however, payers are entitled to real-world evidence regarding benefits of a new medication against existing therapeutic options. Any additional expenditure has to be empirically substantiated on the grounds of data obtained from local population experience.[28,31,33,36,76]

Two specific issues associated with establishing and assessing orphan drug clinical effectiveness may be distinguished. Firstly, there is the selection of a clinical comparator – a conventional therapy that is accessible and paid for with public funds. To a major extent this selection predetermines HTA outcome. Comparison should be made on the basis of adopted common clinical practice while accounting for evidence-based medical approaches. In essence, such an assessment represents a comparative analysis of at least two health technologies and the respective outcomes. When a new medicinal product falls into a well-known therapeutic class, it is easy to compare its efficacy with medications in the same category. The majority of orphan drugs, however, belong to a new therapeutic group in its own right. Hence, comparison is difficult and creates an additional risk of subjectivity with respect to reimbursement. A perception exists among HTA agencies that innovative medications should be assessed by default in view of their innovative nature. The supporting argument is that quite often these therapies are the very first medical response to unsatisfied and unmet needs of patients with severe life-threatening conditions.[77-79]

Secondly, health outcomes reporting – whether to report final outcomes or use the so-called surrogate markers. Due to their rather forecasting nature, surrogate outcomes often fail to predict adequately the consequences of a health technology application and detect correctly the differences between competitive health technologies. Quite logically, regulatory authorities perceive the burden of proof as unsatisfactory. Nonetheless, use of surrogate markers in oncological and rare diseases should not be rejected entirely as an option.[37,78] Health authorities should accept the fact that in situation where the volume of clinical data is small, uncertainty is inevitable. A possible risk management approach would be to introduce additional assessment factors, such

as safety profile of the innovative therapy, self-assessment of patient's quality of life, etc. That is a way to account also for patient's point of view.[44,47,76]

Implementation of the principles of evidence-based medicine in the process of health policy making and in particular, in HTA, brings about a substantial improvement but creates conflicts as well, because a deed good enough for an individual may not be good enough for the whole society. A balance between timely access to innovative therapies, on the one hand, and guarantees for quality, clinical effectiveness and cost-effectiveness, on the other hand, should be sought for. It should be remembered, that in their better part, rare diseases are life-threatening, and prompt initiation of an adequate treatment is crucial.[34-36] However, the taxpayer being the principal financial source of the health system and its end-user, requires quality and efficiency. In this case, a wise solution would be to use flexible criteria to evaluate the clinical value-added of innovative therapies. The regulatory requirement for reliable clinical evidence should go hand in hand with an actual opportunity to acquire such evidence. A well-planned and conducted post-marketing surveillance coupled with epidemiological registers produce results that health authorities can use for an objective cost-effectiveness analysis of orphan drugs.[39-30,42,44]

4.1.4. Cost-effectiveness of orphan drugs

Incremental cost-effectiveness ratio (ICER) is the main economic parameter drawn from HTA. ICER compares a health technology with another one that has the same therapeutic intent and indication, and is already accessible and applied by the health system. The indicator juxtaposes difference in costs with difference in outcomes achieved, or additional costs to be incurred to gain additional outcomes from applying the new technology. While ratio determination in itself requires therapeutically comparable technologies, once calculated, the ratios for various technologies with diverse purposes may be compared and ranked. In this way health authorities may plan and prioritize cost items in healthcare. The single condition here is to use a universal assessment scale for measuring the health outcomes. The most commonly used measuring unit is quality-adjusted life year (QALY).[80-82]

ICER serves as guidance to health authorities when they appraise innovative health technologies and decide on reimbursement with public funds. For instance, 85% of reimbursement recommendations of the National Institute for Health and Care

Excellence (NICE) are substantiated by ICER. In view of orphan drug specifics, it is highly unlikely for them to meet the standard regulatory requirements for cost-effectiveness. It is not because of the methodology used for economic evaluation but rather of the high price and evidence uncertainty of innovative therapies for rare disease. Here the question is whether ICER, employed effectively in conventional health technologies, can be applied directly to orphan drug assessment. Despite the strong public interest in well-argued and transparent decisions for health technology payments with public funds, there are very few examples of formally adopted ICER upper limits. NICE is repeatedly singled out as an institution applying such a limit (£ 30 000 for 1 gained QALY). The claim is neither confirmed nor denied by the organization.[83-85]

ICER offers a range of theoretical advantages, mostly of an organizational nature – reduced burden on health authorities and payers, consistency and transparency of HTA process, fairness, efficiency and public trust. Nonetheless, implementation of an ICER limit suggests existence of conditions that are not always present. Firstly, there is no sustainable, context-independent willingness-to-pay on the part of payers for any additional QALY unit. Reimbursement decision-makers and society as a whole tend to give different priority to health technologies. For instance, all other things being equal, QALY gains to patients with severe life-threatening diseases or to children are perceived to be of higher priority. Absence of an ICER limit provides health authorities with higher flexibility to account for considerations such as equality and social fairness when allocating public funds to healthcare. At the end of the day, HTA is not only about calculating cost-effectiveness and setting payment cap. Any such evaluation should be based on a balance between public and individual interest of patients affected.[81,86-87]

While in the recent past ICER has been regarded predominantly as an argument against recommending reimbursement with public funds, nowadays a number of HTA agencies and payers are reconsidering their position. In the search of an effective expenditure control paralleled with access to innovative treatment, stakeholders increasingly embark on interpreting ICER as a starting point for additional cooperation with physicians, patients and industry rather than as an indicator for an absolute limit of public funding.[88] This explains the growing interest in various alternative approaches for assessment, reimbursement decision-making and access to innovative therapies. The mechanisms include the so-called risk-sharing agreements. They allow for securing financial stability of the healthcare system. The approach is not to the detriment of

patients. On the contrary, it sets conditions enabling access to an innovative treatment. Rare disease patients are given an opportunity to receive a life-sustaining treatment. Valuable information about clinical effectiveness and cost-effectiveness of a health technology pertinent to the specifics of local population and health system is obtained. And not least, health authorities can make an objective, precise and comprehensive appraisal of a technology and take an effective decision for an optimal access to it. Flexible models for assessment and decision-making coupled with epidemiological registers and post-marketing surveillance studies provide a realistic prospect for achieving these objectives.[89]

Establishing clear and transparent criteria for assessment and inclusion of innovative medicinal therapies for rare diseases in the public healthcare coverage is of key importance to ensuring sustainability of healthcare and also to meeting heath needs of these patient groups. Putting this process into an adequate legal framework is appropriate, because it aims to strike a balance and reach agreement between all stakeholders. Any restrictions to health insurance coverage should be analysed carefully, since they may be counter-productive and lead to a serious loss of trust in the healthcare system, as often experienced in practice. If such approaches are employed, they should account for not only fiscal constraints but also any patient's individual right of access to a timely, adequate and quality healthcare service.[90-91]

Theoretical and practical challenges in assessing rare disease medicinal therapies are numerous. Focusing on a single assessment criterion is not an effective solution since it ignores other just as important factors. Not least, absence of sound clinical, epidemiological and economical evidence is in itself a prerequisite to insecure and inadequate access to innovative technologies. Bridging the gap is an important element of assessing rationally such therapies. Adequate solutions may be achieved only if sufficient real-world data about local population are made available. Generalizing evidence from clinical trials up to the stage of acquiring a marketing authorization is far from exhausting all that is needed. This is a long process that requires a multilateral collaboration and coordination. A potential, mutually beneficial solution to all parties involved is to subject innovative therapies for rare disease to a broad post-marketing surveillance in order to diminish the evidence gap in this area. Approaches such as epidemiological registers, access management schemes, etc., are increasingly proving

their key role in accumulating a critical mass of evidence and experience in support of rationalized assessment and reimbursement decision-making processes.[92-93]

4.2. Component B

4.2.1. NHIF expenditure for medicinal therapies

In the last four years NHIF expenditure for medications has increased (Table 9 and Appendix 2). The figure for 2011 indicates an expenditure of slightly over BGN 524 M; out of it, BGN 31 M or 6.03% for rare diseases. It is worth noting that the actual transfer of rare disease therapies to NHIF occurred in the first quarter of 2011, with the first protocols for granting treatment being approved shortly after that. A the time of transfer of rare disease therapies to NHIF, the list under Regulation 38 contained 28 rare diseases.

Table 9. NHIF total expenditure for medicinal therapies (including for medical devices)

Year	Total expenditure* (in BGN)	Expenditure for rare disease medicinal therapies	Relative share	Number of rare diseases included in Regulation 38
2011	524 471 000	31 613 557**	6.03%**	28
2012	600 370 000	46 539 440	7.75%	29
2013	785 516 000	63 306 206	8.06%	36
2014	954 822 000***	74 538 979***	7.81%***	36

* *Total expenditure includes health insurance payments for medicinal products in home treatment and for diet food for special medical purposes, health insurance payments for medical devices and costs for medicinal therapy in malignant diseases, in compliance with the Law on National Health Insurance Fund Budget for 2014.*

** *2011 was a transitional year when rare disease medicinal therapies were transferred from MoH to NHIF. Actual expenditure reported did not cover the full year since the first protocols for rare disease treatments had been issued by RHIF only in the second quarter of 2011.*

*** *Forecast based on expenditure for the first two quarters of 2014.*

Over the past four years this number has increased reaching 36 by mid-2014. As a logical consequence, the relative share of rare disease expenditure also has moved upward and is expected to grow up to 7.81% by the end of 2014. However, notwithstanding the above, and excluding first year of the period – 2011 – as a transitional year with actual expenditure covering a shorter than year period, it is worth noting that the share of rare disease medication expenditure has maintained constant levels as a percentage rate of all NHIF expenditure for medications.

With respect to the relative share of expenditure for rare disease medicinal therapies, two findings can be outlined. Firstly, as an absolute indicator, it fits perfectly to the average levels reported for other Member States. According to latest impact studies, it ranges within 6% and 8%, i.e. Bulgaria is not excluded from the general trend.[28,32,51-53,55,94-100] Secondly, this indicator maintains a relatively constant value in Bulgaria. Apart from 2011 which is not a full year regarding rare disease expenditure, for 2012 – 2014 the share of expenditure for rare disease therapies fluctuates within 7.75% and 8.06%. The increase observed in 2013 as compared to the previous year is due to the higher number of rare diseases included in Regulation 38 and respectively, therapies entered in the PDL. It is seen that the figure for 2014 remains unaltered and the budget impact marks a slight drop. These data allow for drawing the conclusion that NHIF expenditure for rare diseases does not demonstrate an upward trend.

4.2.2. NHIF expenditure for outpatient medicinal therapies for rare diseases

Expenditure indicators for outpatient medicinal therapy for rare diseases show a large variability among nosological units. To reflect NHIF perspective in the budget impact estimation, the study divides rare diseases into two conditional groups, namely: diseases included in the List of diseases for outpatient treatment under Regulation 38 at the time of transfer of these therapies to the health insurance coverage at the beginning of 2011, and diseases added at a later time. This conditional separation stems from the different level of organizational experience and expertise.

Diseases, such as haemophilia and muscular dystrophy, fall within the first group and, one way or other, have been incorporated in the health system for years. (Table 10).

The second group comprises diseases with an effective therapy being made available and accessible only recently (Table 11). Data for these diseases such as epidemiological, clinical and economical, are usually scarce, which hampers assessment and reimbursement decision-making as well as planning of resource for treatment of patients affected.[94-95,98-99]

Table 10. Rare diseases present in the List at the time of transfer of rare disease therapies to health insurance coverage at the beginning of 2011

ICD-10 code	Disease
D56.1	Beta thalassemia (thalassemia major)
D66, D67, D68.0, D68.2	Coagulation defects
D69.3	Idiopathic thrombocytopenic purpura
E22.0	Acromegaly and pituitary gigantism
E22.8	Other hyperfunction of pituitary gland
E23.0	Hypopituitarism
E23.2	Diabetes insipidus
E24.0	Cushing syndrome of pituitary origin
E27.1	Primary adrenocortical insufficiency
E55.0	Rickets, active
E70.0	Classical phenylketonuria
E72.2	Disorders of urea cycle metabolism
E75.2	Gaucher disease, Fabry disease, Niemann-Pick disease
E83.0	Wilson-Konovalov disease
E83.3	Disorders of phosphorous metabolism
E84	Cystic fibrosis
G70.0	Myastenia gravis
G71.0,G71.1,G71.2,G71.9	Primary muscular disorders
I27.0	Primary pulmonary hypertension
K50.0,K50.1	Crohn disease
L10	Pemphigus
M08	Juvenile arthritis
M30.0	Polyarteritis nodosa
M31.3	Wegener granulomatosis
M33	Dermatopolymyositis
M34	Systemic sclerosis
P27.1	Brochopulmonary dysplasia originating in the perinatal period
Q87.1	Prader-Willi syndrome
Q96	Turner syndrome

Table 11. Rare diseases included in the List after transfer of rare disease therapies to health insurance coverage at the beginning of 2011

ICD-10 code	Disease
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin sub-classes G
D81.2	Severe combined immunodeficiency with low or normal B-cell numbers
D83.8	Other common variable immunodeficiency
D84.1	Defects in the complement system (C1 esterase inhibitor deficiency)
E74.0	Glycogen storage disease
E76	Mucopolysaccharidosis
E85.1	Neuropathic heredofamilial amyloidosis

Following the transfer of rare disease therapies to NHIF, 8 new rare diseases have been added to the List of diseases for outpatient care under Regulation 38. This is a contribution to a total of 78 new patients and an expenditure of BGN 4 M for outpatient care in the second quarter of 2014 (Table 12). In comparison, rare diseases present in the List for outpatient care at the time of transfer from MoH to NHIF account for an expenditure of BGN 13 M for over 4 800 patients.

Table 12. NHIF expenditure for outpatient medicinal therapies for rare diseases (in BGN)

Period	Rare diseases included in the List as of the beginning of 2011		Rare diseases included in the List after the beginning of 2011	
	Total expenditure	Patients treated	Total expenditure	Patients treated
2012 Q1	11 678 641	4 135	-	-
2012 Q2	10 288 767	4 094	-	-
2012 Q3	11 230 301	4 094	-	-
2012 Q4	12 505 820	4 486	835 912	4
2013 Q1	13 795 761	4 557	786 740	4
2013 Q2	13 635 563	4 468	817 192	6
2013 Q3	13 750 820	4 417	1 563 064	40
2013 Q4	15 733 360	4 974	3 223 705	64
2014 Q1	15 702 065	4 967	3 767 210	77
2014 Q2	13 511 373	4 807	4 288 842	78
Average growth rate	5.03%	1.69%	31.33%	64.06%

Looking into the dynamic of these indicators, it is seen that the growth rate of the indications added to the List under Regulation 38 after 2011 is many times higher. Outpatient care expenditure increases by an average of 31% per quarter while the number of patients treated – by 64%. The other rare disease group marks much more modest values, 5% and 2%, respectively (Table 12, Figure 4).

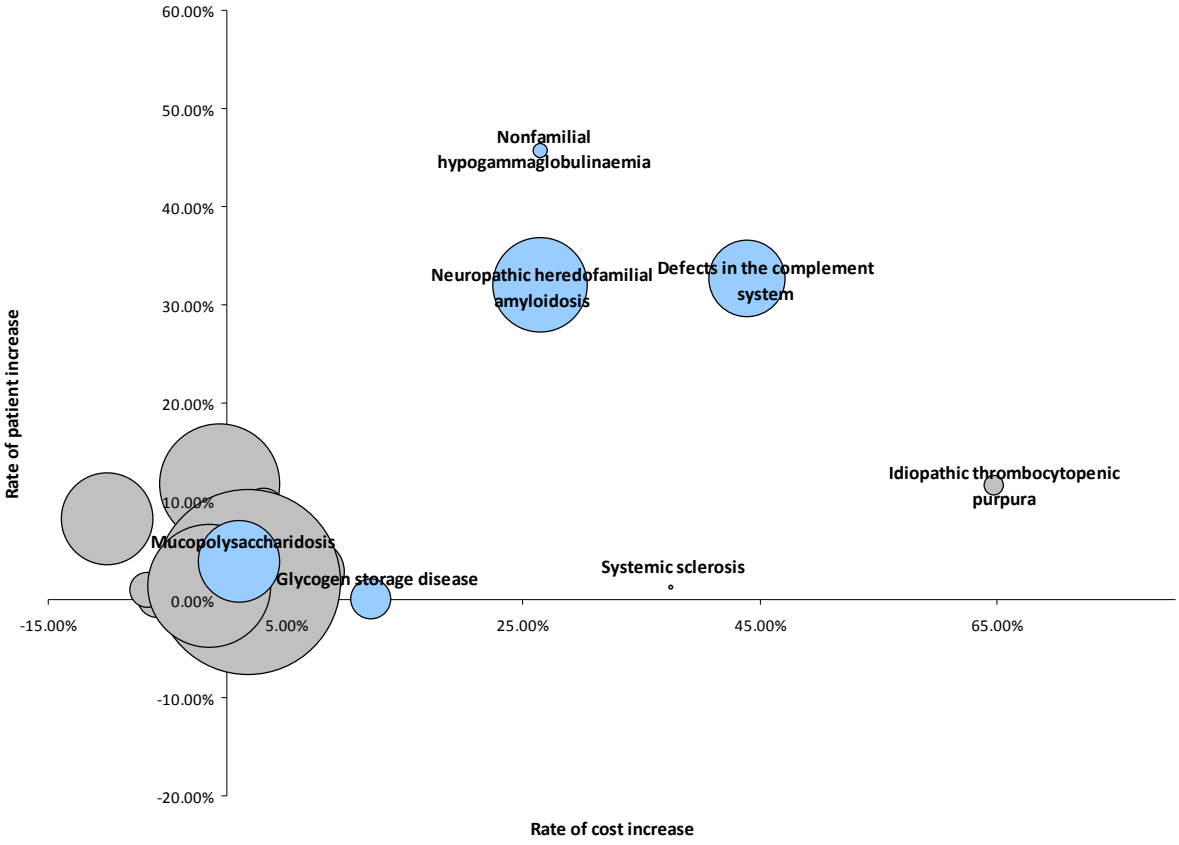

Figure 4. Expenditure developments in rare disease medicinal therapies in Bulgaria for the period 2012-2014

Data reported by health authorities of the five largest EU Member States, Germany, France, the UK, Italy and Spain, showed that 2009 – 2010 expenditure for orphan drugs increased by an average of 13% - 28%, and for utilization – by 7% - 17%.[55] It should be emphasized here that these countries have 80% of orphan drugs made available through their official reimbursement lists. The remaining percentage is covered by alternative access programmes.[33,43,76,79]

Another important point is that access delay is a notion unknown to these countries, while Bulgarian rare disease patients are bound to face delays in starting therapy.[22,30] For years German, French, British, Italian and Spanish rare disease patients have enjoyed a prompt and adequate access to treatment. Logically, expenditure for rare disease therapies is also growing in these countries. With this in mind, it should be noted, that conditions enabling actual and adequate access to rare disease therapies have been put in place in Bulgaria only in the recent years and not for all therapies. Nevertheless, the results of the analysis in Bulgaria point that the growth rate of medicinal therapies' budget impact in the country is smaller than that in other EU Member States.[51,53,55,94,96]

4.2.3. NHIF expenditure per nosological units

The indicators for average expenditure per patient and number of patients treated exhibit dynamical behaviour in all nosological units. This is observed in diseases included in the List for outpatient care under Regulation 38 at the time of transfer to NHIF and in those added at a later stage (Tables 12-14). Surely, all comparisons are quite conditional. The majority of rare diseases affect several organs or system. Organizational experience and expertise level are very diverse.[102-104] Any budget impact dynamic per nosological unit depends, firstly, on two factors: average cost per patient and number of patients treated. Level of access to medicinal therapies and access delays, experience and expertise, availability of therapeutic alternatives and unmet health needs are also pertinent to the final magnitude of a budget impact of a rare disease.[95,100-101,105]

Analysis of indicators for the first rare disease group, namely, those present in the List for outpatient care under Regulation 38 at the time of transfer to NHIF in 2011, shows that the average total expenditure per quarter vary from 8 BGN in Wegener's granulomatosis to 4.4 M BGN in haemophilia (Table 13). As regards expenditure growth rate per patient, two diseases stand out – idiopathic thrombocytopenic purpura and systemic sclerosis. For both of them new therapies have been included in the Positive Drug List during the period 2011 – 2014. As for purpura, this growth is coupled with an increase in the number of patients treated while for systemic sclerosis the number of reimbursed persons remains constant (Figure 5).

A decline in the average expenditure per patient is observed in a large portion of the diseases in this group. (Table 13, Figure 5). This is valid for diseases involving expensive treatment such as beta thalassemia, Gaucher disease, Fabry disease, Niemann-Pick disease, cystic fibrosis, diabetes insipidus, Turner syndrome and Prader-Willi syndrome, as well as for diseases with a more contained budget impact such as myasthenia gravis, Wilson disease, other hyperfunctions of the pituitary grand and disorders of phospohorus metabolism. An even more interesting fact is the slight rise in the number of patients treated that is observed for the majority of diseases. In other words, following therapies' transfer to NHIF, a larger number of patients have access and are treated effectively at a lower price.

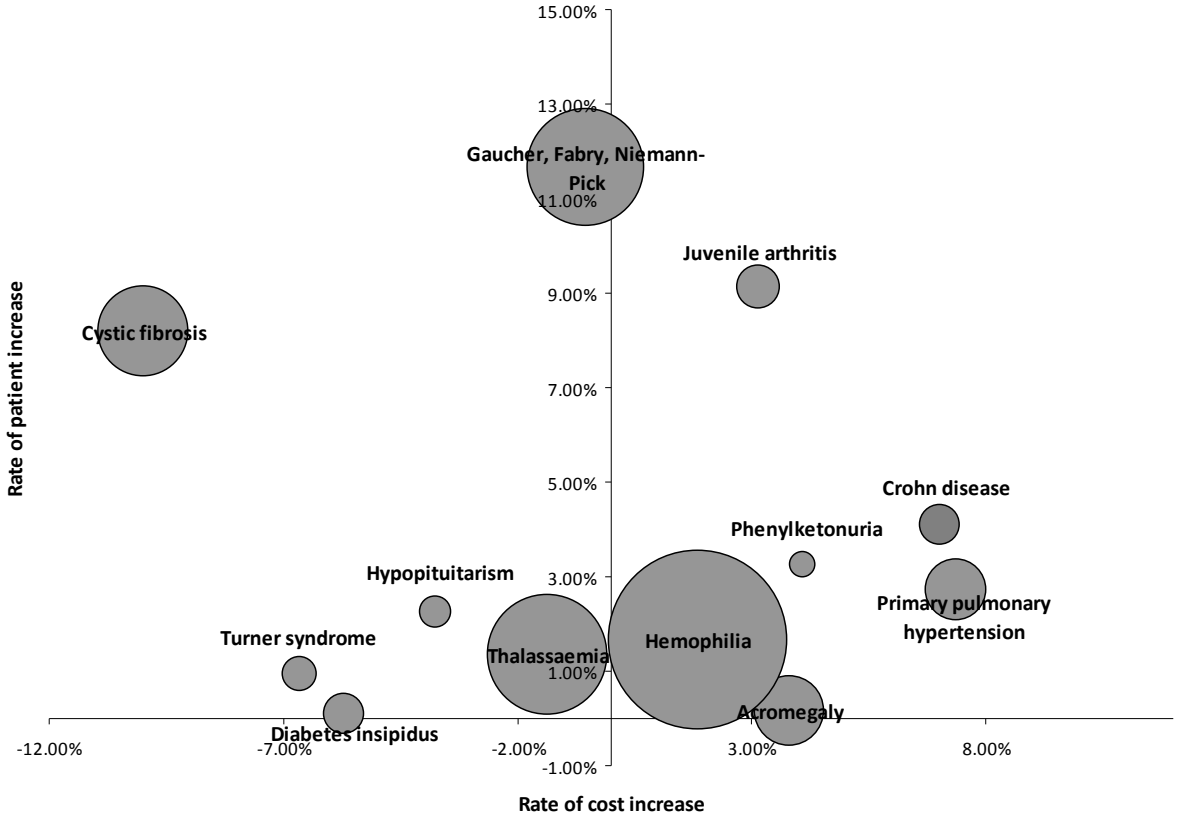

Figure 5. Expenditure developments in rare disease medicinal therapies included in the List at the beginning of 2012

From economic perspective, NHIF pays less and receives more in the form of health outcomes and patients satisfied. This is a key finding because it proves empirically that transfer of rare disease medicinal therapies from MoH to NHIF has been an appropriate move. At the end of the day, patients are content because they have

prompt and adequate access to effective therapies. On its part, NHIF manages the funds allocated to these therapies in a more efficient way – larger number of patients is treated at a lower expenditure level.

Table 13. NHIF quarterly expenditure for outpatient rare disease medicinal therapies included in the List at the beginning of 2011, per nosological unit

Rare disease	Average total expenditure	Average expenditure per patient		Average number of patients treated	
		BGN	Growth rate	BGN	Growth rate
Coagulation disorders	4 440 998	17 588	1.85%	253	1.66%
Beta thalassemia (Thalassemia major)	2 014 926	9 163	-1.36%	220	1.33%
Gaucher disease, Fabry disease, Niemann-Pick disease	1 930 575	87 356	-0.53%	22	11.67%
Cystic fibrosis	1 141 426	5 659	-9.98%	202	8.18%
Acromegaly and pituitary gigantism	676 638	3 280	3.82%	206	0.16%
Primary pulmonary hypertension	548 548	5 415	7.36%	101	2.72%
Juvenile arthritis	264 110	3 167	3.14%	83	9.11%
Crohn disease	262 582	380	7.03%	692	4.09%
Diabetes insipidus	236 264	363	-5.69%	652	0.09%
Turner syndrome	169 626	3 448	-6.66%	49	0.95%
Hypopituitarism	164 204	1 881	-3.75%	87	2.24%
Classical phenylketonuria	111 393	2 130	4.11%	52	3.25%
Myasthenia gravis	93 380	89	-0.30%	1 045	1.13%
Idiopathic thrombocytopenic purpura	58 925	1 830	64.72%	32	11.61%
Disorders of urea cycle metabolism	40 775	4 161	1.25%	10	1.06%
Prader-Willi syndrome	28 605	1 973	0.97%	15	8.01%
Wilson disease	18 767	152	-1.45%	124	0.66%
Other hyperfunction of pituitary gland	15 666	578	-2.60%	27	2.05%
Systemic sclerosis	7 502	79	37.50%	95	1.16%
Primary muscular dystrophy	3 583	83	1.71%	43	-3.71%
Disorders of phosphorus metabolism	1 253	50	-5.46%	25	1.49%
Primary adrenocortical insufficiency	1 107	7	0.00%	169	-0.19%
Pemphogus	561	10	-1.28%	59	-0.58%
Dermatopolymyositis	447	9	-1.16%	52	-0.63%
Cushing syndrome of pituitary origin	333	40	0.78%	8	-2.75%
Poliarteritis nodosa	110	9	-4.07%	12	4.17%
Wegener granulomatosis	8	7	-7.04%	1	0.00%

Analysis of expenditure indicators of outpatient medicinal therapy for rare diseases added to the List under Regulation 38 following transfer to NHIF reveals rather different developments (Table 14).

Table 14. NHIF quarterly expenditure for outpatient rare disease medicinal therapies included in the List at the beginning of 2011, per nosological unit

Rare disease	Average total expenditure	Average expenditure per patient		Average number of patients treated	
		BGN	Growth rate	BGN	Growth rate
Neuropathic heredofamilial amyloidosis	1 189 572	63 444	26.55%	19	32.00%
Mucopolysaccharidosis	893 711	195 499	1.08%	5	3.79%
C1 esterase inhibitor deficiency	779 001	28 327	43.94%	28	32.64%
Glycogen storage disease	234 788	117 394	12.20%	2	0.00%
Nonfamilial hypogammaglobulinemia	37 288	5 483	26.55%	7	45.65%
Other common variable immunodeficiency	4 566	2 283	22.46%	2	0.00%
Selective deficiency of immunoglobulin G	1 787	1 787	0.00%	1	0.00%
Severe combined immunodeficiency with low or normal B-cell numbers	1 489	1 489	0.00%	1	0.00%

Here, the average expenditure per patient is considerably higher. In absolute values, mucopolysaccharidosis and glycogen storage disease are the two rare diseases that cost the most per patient out of all rare diseases covered by NHIF under its outpatient care list. Neuropathic heredofamilial amyloidosis and C1 esterase inhibitor deficiency rank forth and fifth, respectively.

More attention should be paid to the developments of expenditure indicators. With the exception of some congenital immunodeficiencies and mucopolysaccharidosis, all diseases in this group show a double-digit expenditure growth per patient. C1 esterase inhibitor deficiency, especially, stands out with a close to 44% quarterly expenditure growth per patient. The picture is complemented by a significant growth in the number of patients reimbursed – for three of the diseases, this indicator ranges between 32% and 46%. In order to facilitate NHIF budget management and secure overall fiscal stability of the Bulgarian health system, such an uncertainty in the developments should be addressed by a set of measures, including measures for financial risk-sharing.

4.2.4 Trends in expenditure developments of rare disease therapies

In view of the increasing number of rare disease therapies approved and authorized for use, European measures to encourage research and development of orphan drugs can be defined as an undisputable success story. A consequence of the story, however, is the increasing budget impact of rare disease therapies. All analyses and publications are unanimous about two findings: rare disease treatment expenditure will continue to rise and an increasing number of new medicinal products will be approved for use.[51-53] Some more conservative views stipulate that generic medicines will replace currently available products when patents expire, and marketing authorization approval will be less successful and market penetration rate will diminish.[51,53] The USA has now a 30 year experience in the area of orphan drugs. In fact, EU orphan drug legislation framework has been drawn on the USA's. Opening American market to generic medicines has caused price erosion ranging from 5% to 95%.[51] There are two generic medications registered in Bulgaria and included in PDL. Their price is about 20% lower. In any case, forecasts on budget impact should take into account EC efforts to foster new rare disease therapy development. The largest ongoing development is undertaken by the International Rare Disease Research Consortium (IRDiRC), being a joint initiative with the US National Health Institutes. The Consortium coordinates investments in rare diseases with two clear objectives: by 2020, to create 200 new therapies and develop diagnostic tools for the majority of rare diseases.[13,23,69-73,75,104-105]

The principal budget impact determinants are well known: number of patients treated and expenditure per patient. However, the current analysis confirms two important trends in the expenditure for rare disease medicinal therapies. Under realistic conditions, budget impact depends to a major extent on availability and accessibility of effective therapies.[4,22,30-32,35,47,48,51,53,65,94]

Firstly, a key factor affecting budget impact magnitude of new rare disease therapies are marketing authorizations and most of all, decisions on reimbursement of new therapies with public funds.[22,30-32,94] It is highly unlikely to have only one patient with Wegener granulomatosis in Bulgaria. But without available and accessible innovative therapies, such patients do not have an incentive to address the health system. Similar considerations are valid for patients with primary muscular disorders, whose number shows the largest downward pace in the years 2011 – 2014. Unavailability of an efficient

therapy capable of reversing the course of their disease can hardly motivate patients to turn to the health system. It is likely for some of them to register under different diagnoses so that medicinal therapies are covered by the health system or health insurance funds.[17,106] However, what is more important here is that if there are no available and accessible therapies, such patients and their families will endure loss of quality of life, high morbidity and premature death. For society this means high socio-economic burden, lost of human potential and not least, loss of trust in the health system and poor perception of system operations.[107-110] According to European surveys, direct costs are just a tiny portion (between one quarter and one third) of the losses borne by Member States as a result of rare diseases.[17,111-113]

Undoubtedly, innovative therapies introduced and included in the health insurance coverage affect expenditure volume and number of patients treated. Examples to that end are idiopathic thrombocytopenic purpura and systemic sclerosis which have been part of the List for outpatient care at the time of transfer to NHIF (2011). However, this is not a typical situation for Bulgaria or for rare diseases only, for that matter. A similar phenomenon is observed globally. Expenditure and number of patients start moving upward any time innovative therapies become available. In itself, this encourages diagnosis and physicians' awareness.[114] Here, however, it is important to consider the problem from the perspective of patients and their families. Over the last decades advancements in medical science have been huge. Today, numerous diagnoses with lethal outcome are transformed into manageable chronic conditions, permitting patients to lead a complete private and social life. In this context, innovative therapies are an extremely good investment from societal perspective because, on the one hand, they support the most vulnerable and weakest society members and on the other hand, they make sure large socio-economic losses associated with high morbidity and mortality due to rare diseases are avoided.[17,107,109-113]

Secondly, data indicate that even for rare diseases such as haemophilia which has been studied extensively and effective therapies have been made available and accessible since long, expenditure volume and number of patients also show an unpside trend with time. This can be explained from both clinical and historical perspective. For the majority of rare diseases the therapeutic dose is determined on the basis of patient's weight. When the patient matures and the therapy gives results, i.e. the patient is in good health, the dose also increases, which means that the average expenditure per

patient also rises. It is a consequence of therapy effectiveness and is an indicator for expediency of treatment expenditure.[115-116] For Bulgaria, another important reason for this trend happens to be lack of diagnosis, unsuitable treatment and limited access to rare disease treatment (from historical perspective). In fact, the latter two have prompted transfer of outpatient care medicinal therapies for rare diseases from MoH annual centralized tenders to the mandatory health insurance coverage. The improved access provides a more effective treatment of rare disease patients in Bulgaria and extends their life expectancy and quality of life.[30] Average expenditure growth comes as a logical consequence but it remains within reasonable limits and is comparable to NHIF expenditure developments for other disease groups.

Not least, expenditure developments are linked to and will depend on European integration processes in the future. EC has taken on some serious commitments in the area of rare diseases spanning up to 2020. They will be reflected in both, new therapies introduced in Member States and improved awareness and knowledge of medical professionals. At national level, the outcome will be enhanced access to adequate medical and health care.[7-9,13,23,71-73] Bulgaria should support the common European policy in this area, and should foster successful domestic experience, including provision of guarantees for equal and non-discriminatory access to effective medicinal therapies for rare disease patients.

4.2.5. Expenditure management of rare disease therapies

Budget impact magnitude and dynamic of rare disease medicinal therapies are poorly studied in Bulgaria and Eastern Europe. However, some other countries have already implemented successful policies for expenditure management. For instance, in Belgium public expenditure for medications has a limit. Two-thirds of the overspending is covered by the pharmaceutical industry while the remaining portion – by the National Health Insurance Institute (Institut National d'Assurance Maladie-Invalidité, INAMI).[94] INAMI is the principal payer in Belgium and can enforce various clauses about medication expenditure limits and medication reimbursement.[33] Similar risk-sharing agreements are applied in an increasing number of countries due to the financial pressure exercised by the rising costs of innovative health technologies and the payers' desire to have a more secure and efficient public healthcare system.[33,117-133]

Innovative rare disease therapies are an excellent candidate for risk-sharing agreements. One of the earliest examples of such an agreement dates back to 2004 when the Department of Health in Australia agreed to reimburse bosentan under the condition that a register for patients with primary pulmonary hypertension would be created and the future reimbursement price would take into account its outcomes.[126] A key detail in risk-sharing agreements is reliability and quality of information collected in registers following a positive reimbursement decision taken by health authorities. Italy is one of the most experienced countries in this area, applying such agreements since 2006. The Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) manages clinical and financial supervision mechanisms in real time via web-based registers. AIFA maintains registers for over 80 diseases (including rare diseases), covering more than 400 000 patients.[127]

In Eastern Europe, risk-sharing mechanisms have a relatively young history.[128-129] In the context of international reference pricing of medicinal products and a small market share, Eastern European countries have very few leverages to influence pricing and reimbursement processes, despite their objective need to purchase medicinal products at a lower price due to existing financial constraints.[129] From this stand point, risk-sharing agreements are of crucial importance to these countries. Such mechanisms can secure access to new rare disease therapies without raising the financial risks for the public health insurance system.

Certainly, numerous challenges remain to be faced such as lack of relevant legal framework, lack of expertise and underdeveloped scientific infrastructure.[33,118-122,128,134] Nonetheless, since expenditure will continue to rise, Eastern European countries and Bulgaria, in particular, should conduct an in-depth risk-benefit analysis of these approaches, seek proactively international cooperation and take the best decision to the interest of rare disease patients and the health system as a whole.[33,121,128-129]

Indeed, expenditure for rare disease treatments puts pressure on national healthcare budgets. Payers have limited resources available and any unplanned increase in number of patients treated and/or cost per patient may lead to a substantial deficit. When rare disease therapies became part of the mandatory health insurance (2011), NHIF took measures to control uncertainty of expenditure. Whereas, risk-sharing agreements are yet to be legally regulated in Bulgaria, NHIF has implemented a mechanism, well-known in scientific literature as conditional treatment continuation.[117,120]

Protocols for outpatient care medicinal therapy are granted a continuation only if defined therapeutic outcomes are achieved. This model makes sure that patients on an efficient therapy remain on the same treatment. In this way health authorities are protected from covering for therapies that do not show actual clinical benefits.[33,117]

A serious setback in the mechanisms put in place by NHIF thus far is the absence of an effective management of overspending risk. Healthcare expenditure, including for rare diseases, will continue to increase for various reasons (population aging, increased prevalence of chronic non-communicable diseases, medical science advancements, etc.).[33,46,51,53-54,76,82,117] Therefore, linking reimbursement to clinical performance is, in itself, insufficient. NHIF needs tools to address the risk of overspending. Such tools should be developed in conjunction with other stakeholders.

4.3. Component C

4.3.1. Profile of survey respondents

The survey engaged 16 respondents from 10 Member States (Table 15). They represented a broad range of institutions, the majority being directly involved in registration, pricing, assessment and reimbursement of rare disease therapies. The sample was balanced in terms of geographical representation – there were respondents from Western, Southern, Central and Eastern Europe.

Table 15. Survey respondents profile by Member State and institution

Country	Institution	Institution profile
Austria	Ludwig Boltzmann Institut für Health Technology Assessment	Academic organization
Austria	Non-afiliated expert	-
Belgium	Institut national de l'assurance maladie-invalidité	Health authorities
UK (England)	National Health Service	Health authorities
UK (Scotland)	Scottish Medicines Consortium	Health authorities
Germany	Gemeinsamer Bundesausschuss	Health authorities
Germany	Hochschule für Angewandte Wissenschaften Hamburg	Academic organization
Denmark	Syddansk Universitet	Academic organization
Spain	Instituto de Salud Carlos III	Health authorities
Spain	Agencia Española de Medicamentos y Productos Sanitarios	Health authorities
Italy	Agenzia Italiana del Farmaco	Health authorities
Italy	Istituto Superiore di Sanità	Health authorities
Poland	Agencja Oceny Technologii Medycznych	Health authorities
Poland	Non-afiliated expert	-
Netherlands	Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie	Health authorities
Czech Republic	Státní ústav pro kontrolu léčiv	Health authorities

Responses of Eastern European representatives have been considered with particular interest due to several common characteristics shared by the health authorities in these countries and Bulgaria. The advancement of Poland in the area of drug regulation is impressive. Poland is among the first Eastern European countries to set up its own Health Technology Assessment Agency (Agencja Oceny Technologii Medycznych, AOTM). Today, Polish stakeholders deem this act to be a serious success.[135-141]

AOTM was established in 2005 as an advisory body to the Polish Ministry of Health. In 2009 it gained the status of an independence legal entity. The main objective of the organization is to draw up statements about financing health technologies with public funds (medications, interventions, devices, programmes). AOTM assessment reports and recommendations are based on additional officially published data, expert opinions, and information provided by manufacturers and the Polish Health Insurance Fund. Along with reviewing external reports, AOTM is entitled to producing its own reports on health technology assessment upon an explicitly expressed public interest. The institution is in charge of drawing up, publishing and disseminating methodologies and guidelines on health technology assessment.[135-139]

AOTM is managed by a President. There is a 10-member Consultative Council composed of independent experts appointed by the Minister of Health. The President and the Council approve organization statements, while overseeing their correctness and objectivity. Prior to that, a team of analysts reviews documents submitted to make sure that official guidelines and requirements on health technology assessment are complied with. Any final statement accounts also for context-dependent factors such as clinical alternative, social impact, organizational implications, public priorities, and ethical aspects. [135,140-141]

AOTM works in close cooperation with European and international organizations on health technology assessment issues such as Health Technology Assessment International (HTAi), International Network of Agencies for Health Technology Assessment (INAHTA), ISPOR, and European Network for Health Technology Assessment (EUnetHTA). AOTM is an active participant in a series of European programmes and reference networks. AOTM operates with a team of about 60 professionals in various fields. Organization's annual budget is approximately € 2.45 M.[135,140]

4.3.2. Good practices for orphan drug registration, assessment and reimbursement in Europe

Medicinal products with a orphan designation status, are subject to an EMA centralized procedure for marketing authorization and registration, i.e. they do not require further registration in Member States.[2,29] Nonetheless, some Member States (Austria, Denmark, Spain) require from the marketing authorization holder to submit documents for registration to the respective national health authorities. In itself, this is a formality but causes delays in patient access to treatment. In Spain, orphan drugs cannot be used before the entire pricing process is completed.

As regard pricing, Member States apply a whole range of measures, including external and internal reference, price control, free negotiation, value-added pricing, etc. [142-143] It should be noted that health authorities employ mechanisms of various strength when negotiating medicinal product prices. Certainly, all of them aim at acquiring the lowest possible price since healthcare resources are limited and health needs are growing. Under these circumstances, large countries are in a more privileged position. Firstly, their market is larger and more importantly, their positive drug list holds a core position in the currently applied approach of international reference pricing of medicinal products. In this context, industry is more prone to compromise and make concessions when registering a product in such a country.[129]

Price control exercised by means of the pricing process is mandatory when the product applies for a reimbursement with public funds.[144] In Germany and France, health authorities are prepared to accept a higher price and a higher reimbursement rate when a new medicinal product demonstrates higher clinical value-added. And vice versa, if a product does not demonstrate supremacy against competitive agents, the only way to enter it in the positive drug list is to offer a lower price.[38,79] The issue of clinical comparators and therapeutic alternatives, however, is rather complicated when in comes to rare disease medicinal therapies, in particular, orphan drugs. As per the definition, and the official EMA terminology, orphan drugs represent the first real alternative for rare disease patients and/or offer significant health benefits compared with medicinal products available currently.[31] That is why, for instance, in Germany, an orphan designation is considered automatically equal to therapeutic supremacy. However, supporting evidence should be collected and submitted when a turnover of € 50 M is reached. Monitoring and assessing epidemiological, clinical and economic data form an

essential part of pricing strategy in Italy, where price assigned to product should be defended with real-world data.

For reasons mentioned earlier, smaller countries have fewer options for medicinal therapy pricing, in general. International reference pricing of medicinal products remains to be the most widely used pricing mechanism in Eastern Europe. Faced with economic problems, these countries try to implement other measures as well. A knee-jerk reaction is to set various limits per patient or product. This, however, is a mixed-blessing endeavour. There is some sort of a control exercised on public health expenditure but the negative effect on both patient access to treatment and health system efficiency, is strong and long-lasting.[143-144] That is why smaller countries adopt more flexible strategies for pricing and reimbursement of rare disease medicinal therapies, namely, risk-sharing agreements. The latter are gaining pace in countries like Poland, Hungary, the Czech Republic, Slovakia, etc.

The second important stage in the process of securing access to rare disease medicinal therapies is assessment and reimbursement decision-making. Any EMA marketing authorization is issued following a review of product clinical efficacy based on risk-benefit analysis. However, Member State national authorities and most of all, payers, require data about clinical effectiveness of a therapy obtained locally.[145-147] Therefore, health authorities demand additional data to be collected via post-marketing surveillance studies and registers. This is reasonable in view of the relatively high price of the medicinal products in question and the accompanying uncertainty as to rare disease epidemiology, clinical effectiveness confirmed by local experience and final costs of therapy application. All this prompts health authorities to be very causious.[146-150]

Rare disease registers are now a booming exercise in Europe.[40,65] As indicated by the European portal for rare diseases, Orphanet, by 2014 the number of rare disease registers in Member States has reached 641.[151] Growing interest in rare disease epidemiology will boost further increase. This can be attributed to the adoption of national rare disease policies and the implementation of flexible mechanisms to manage access to rare disease innovative therapies.[13,23,44,71,78] Registers and in general, studies of epidemiological, clinical and economic aspects form an integral part of risk-sharing agreements. Generation and collection of such data is a highly specialized activity requiring sound expertise, European collaboration and not least, adequate infrastructure.[30,34,38,43,47,65,92]

Bulgaria is the 'excellent student' of Eastern Europe regarding rare disease registers. Orphanet data reveal that under this item, the country ranks first in the region and 10th in EU, i.e. Bulgaria is positioned among the largest Member States operating substantial financial and human resources, and having long-term experience.[151] An important detail here is that while countries like Italy, Spain and France perceive rare disease registers as a public health priority, in Bulgaria, the majority of registers come as a result of the independent efforts of non-governmental organizations, such as the Institute for Rare Diseases, of medical scientific societies and patient organizations.[64] In the context of reimbursement decision-making for rare diseases this means that should risk-sharing agreements be formalized, Bulgaria will have expertise accumulated via post-marketing surveillance and registers. Health authorities and stakeholders should use knowledge gathered in an expedient manner, even more so under the assumption that global experience and expertise in rare diseases and orphan drugs are rather scarce. [30,34,38,47,65]

It is only after passing successfully through the process of registration, pricing, assessment and reimbursement decision-making, that it is possible to talk about providing access to rare disease medicinal therapies. This process is country-specific and it is rather difficult to estimate its duration in the different countries (Tables 16-19).

Table 16. Time delay in access to idursulfase (orphan drug for mucopolysaccharidosis type II)

Date of EU marketing authorization	**08.01.2007**	**Time delay in access, in months**
Member State	**Data of access decision**	
Bulgaria	05/2012	65
England and Wales	04/2007	4
Italy	03/2011	51
Poland	01/2008	12
Netherlands	05/2007	5
Belgium	01/2008	12
Czech Republic	05/2008	16

A 2012 survey conducted in Bulgaria shows an average time delay of 43 ± 29.1 months.[30] Since then, however, a number of legislative amendments and organizational changes have taken place, aiming to shorten this period, though indirectly.[38]

Table 17. Time delay in access to sapropterin (orphan drug for phenylketonuria)

Date of EU marketing authorization	02.12.2008	Time delay in access, in months
Member State	Data of access decision	
Bulgaria	07/2013	55
England and Wales	04/2013	52
Italy	07/2009	7
Poland	-	-
Netherlands	06/2009	6
Belgium	07/2010	19
Czech Republic	07/2013	55

An idea of how diverse and complex this process can be in different Member States is given by the data on time delay in access to a sample of orphan drugs with a marketing authorization granted over the recent years (Tables 16-19). As it is seen, it is no uncommon to have situations where a medication is accessible and reimbursed in a given country while in another – it is not.[31-35,51]

Table 18. Time delay in access to tafamidis (orphan drug for neuropathic heredofamilial amyloidosis)

Date of EU marketing authorization	16.11.2011	Time delay in access, in months
Member State	Data of access decision	
Bulgaria	05/2013	18
England and Wales	-	-
Italy	05/2013	18
Poland	-	-
Netherlands	02/2012	3
Belgium	01/2014	25
Czech Republic	-	-

However, something else attracts immediate attention – countries like the Netherlands, the UK and Italy operate on a very short timeline for granting access to rare disease treatment. Very often a positive reimbursement decision is taken within a year after an EMA issued marketing authorization. On the contrary, in Bulgaria, the

Czech Republic and Poland, this process may take years and at the end of the day, it is patients and their families that bear the consequence. (Tables 16-19).

Table 19. Time delay in access to ambrisentan (orphan drug for primary pulmonary hypertension)

Date of EU marketing authorization	21.04.2008	Time delay in access, in months
Member State	**Data of access decision**	
Bulgaria	08/2011	40
England and Wales	08/2008	4
Italy	02/2009	10
Poland	01/2013	56
Netherlands	08/2008	4
Belgium	02/2009	10
Czech Republic	06/2012	50

Delay in access to treatment is quite an important factor because it is about severe, life-threatening and/or debilitating conditions where timely diagnosis and adequate access to treatment are crucial. Both indicators – number of rare disease accessible therapies and delay in access to such therapies – describe very precisely whether patients are granted equal and fair access to treatment.[3-5,9,17,22] At the end of the day, the most important outcome of all policies on rare diseases and orphan drugs should be extended life expectancy and improved quality of life of rare disease patients. The latter two depend also on a timely intake of an effective therapy. [38,47,74]

Member States employ diverse approaches to tackle funding of rare disease therapies.[146] In countries like the UK, Belgium and the Netherlands, where health systems are publicly accessible, health authorities pay for rare disease treatments and orphan drug therapies. In Italy, this responsibility is shared between national and regional authorities, while in Spain – it is entirely in the hands of regions. In Germany, Austria, Poland and the Czech Republic, the health insurance funds pay for rare disease therapies. Some of the countries employ targeted state funding for individual diseases, such as haemophilia in Poland. Apart from officially accessible therapies, there are some public solidarity funds in Italy, Belgium and the UK (Scotland) that cover for treatment with non-reimbursed medications. Such funds are mostly used to pay for the treatment in the interim period between acquiring an EU marketing authorization and a

reimbursement decision of the national authority. This overcomes delay in access to therapy which otherwise may have some irreversible and even fatal consequences for patients.[147,150]

Looking into the entire set of indicators for access to rare disease therapies and in particular, to orphan drugs, it becomes apparent that over 80% of these products are included in the reimbursement lists of Western and Central European countries. The remaining portion is made available to patients via several programmes for alternative access. In addition, patients have also access to compassionate use schemes.[152] In any case, patients are not required to pay for these therapies. It is the health authorities, health insurance funds and other sources that finance patients' treatment. Apart from granting equal and adequate access to all patients regardless whether they suffer from a rare or frequent illness, health authorities ensure preservation of patients' and their families' dignity at times of health hardships. This is a way to maintain not only high level of trust in the health system but also secure its long-term sustainability because society feels satisfied with system operations.[4,14,30,33,43,76]

4.3.3. Linking acces to health outcomes

Rational and adequate use of health technologies, including medications, has to balance the interests of principal stakeholders against a background of an increasing budget pressure and epidemiological, clinical and fiscal uncertainty.[153] In this dynamic context, health authorities look for new mechanisms to manage risk and make the best out of expenditure made. All countries demonstrate enthusiasm about linking medicinal product reimbursement and payments to collecting additional evidence and/or measuring health outcomes and benefits in the 'real-world', i.e. outside the context of randomized controlled clinical trials.[124,154]

Contemporary public healthcare understands risk-sharing as tying reimbursement status of a health technology to concrete outcomes of technology use. Risk-sharing agreements are a contract between a payer and a manufacturer where price, level and nature of reimbursement are linked to future outcomes about patients' life expectancy and quality of life.[116] A significant operational element of these agreements is setting up a plan by which the performance of the medicinal product is tracked in a defined patient population over a specified period of time and the level of continuation of reimbursement is based on the health and economic outcomes achieved.[152] The basic intent of such

arrangements is the commitment to secure prompt and adequate access of patients to innovative and potentially beneficial therapies in an environment marked by significant uncertainly and financial risk.[33,118]

Orphan drugs and rare disease innovative therapies in general, being of a very specific nature, are the perfect candidate for such type of agreements.[126,130] The limited volume of epidemiological, clinical and economic evidence within the period immediately following placement on the market is the main reason for heath authorities to be concerned about the actual impact of these therapies, with respect to both health benefits to patients and actual budget expenditure.[94,124] The relatively high price and unclear epidemiological picture are prerequisites for a high risk which, in fact, justifies the need to seek for a balance of interests of all stakeholders.[88,101,119]

The move towards risk-sharing agreements observed is driven by the eagerness to achieve adequate access while ensuring stability and long-term sustainability of the healthcare and health insurance system. Two are the trends describing the process in contemporary public health – tying reimbursement status with additional epidemiological, clinical and economic evidence from real-world experience and apply and constantly improve access to innovative therapies based on post-marketing surveillance data.[33,47,77,88,94,117]

4.3.4. Risk-sharing agreements

There is no uniform approach to defining various types of risk-sharing agreements. These mechanisms come under numerous different names: risk-sharing, performance-based payments, coverage with evidence development, evidence-based reimbursement, etc. In the majority of case, it is about close, overlapping concepts.[117-134]

When categorizing risk-sharing agreements, an important point is the type of outcomes against which coverage is negotiated.[117,153] These outcomes may be health-based, i.e. linked to achieving and/or proving clinical benefits to a defined patient population over a specified period of time, or non-health-based, i.e. linked to negotiated price and/or cost rates (Figure 5). The latter do not differ much from the currently applied approaches for managing budget impact of various health technologies. They can be initiated at a population level in the form of an agreed market share and volume of sales, and at an individual level by means of various restrictions to patients.[127] In this approach, the leading and single considerations are the fiscal ones. Improved patient

access or more effective spending of health funds is out of the question. This is more of a knee-jerk reaction measure which leads to temporary solutions without sound benefits and long-term sustainability of the payer.[128-129] Some definitions of risk-sharing even exclude reimbursement schemes where the payment rate is not tied to achieving and confirming specific health outcomes.[117,126-127,130] Generation of new epidemiological, clinical and economic evidence proves to be of key importance to effective application of risk-sharing agreements in contemporary health insurance.

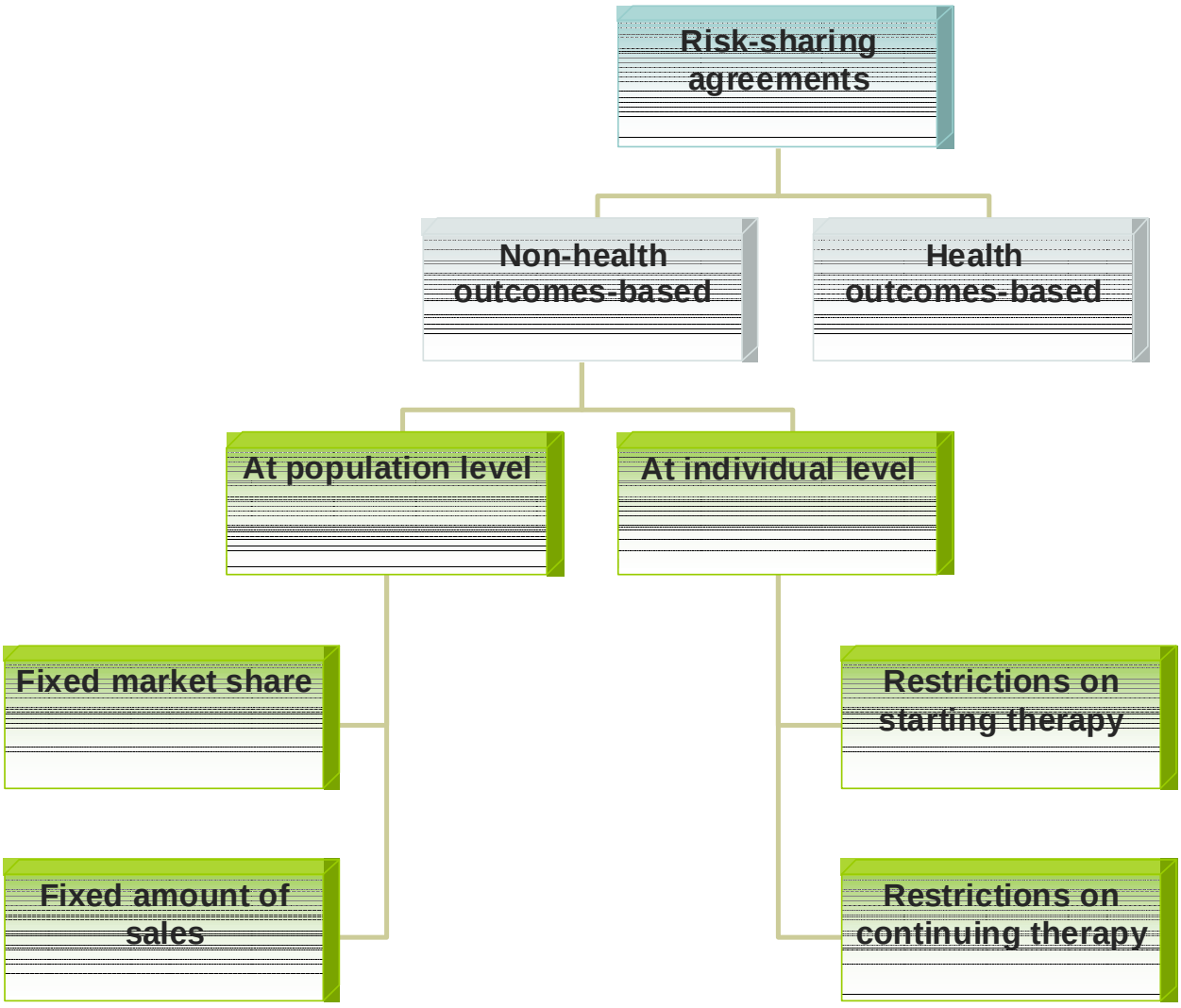

Figure 5. Classification of non-health outcomes-based risk-sharing agreements
Adapted from Carlson et al. (2010)[117] & Morel et al. (2013)[33]

Health outcomes-based risk-sharing agreements may be divided in two categories (Figure 6).[117,153] The first one is the so-called conditional coverage by the public health system which sets a reimbursement requirement to initiate a programme

for data collection (register) in support of taking an informed decision on the use of a health technology in a real environment.[88]

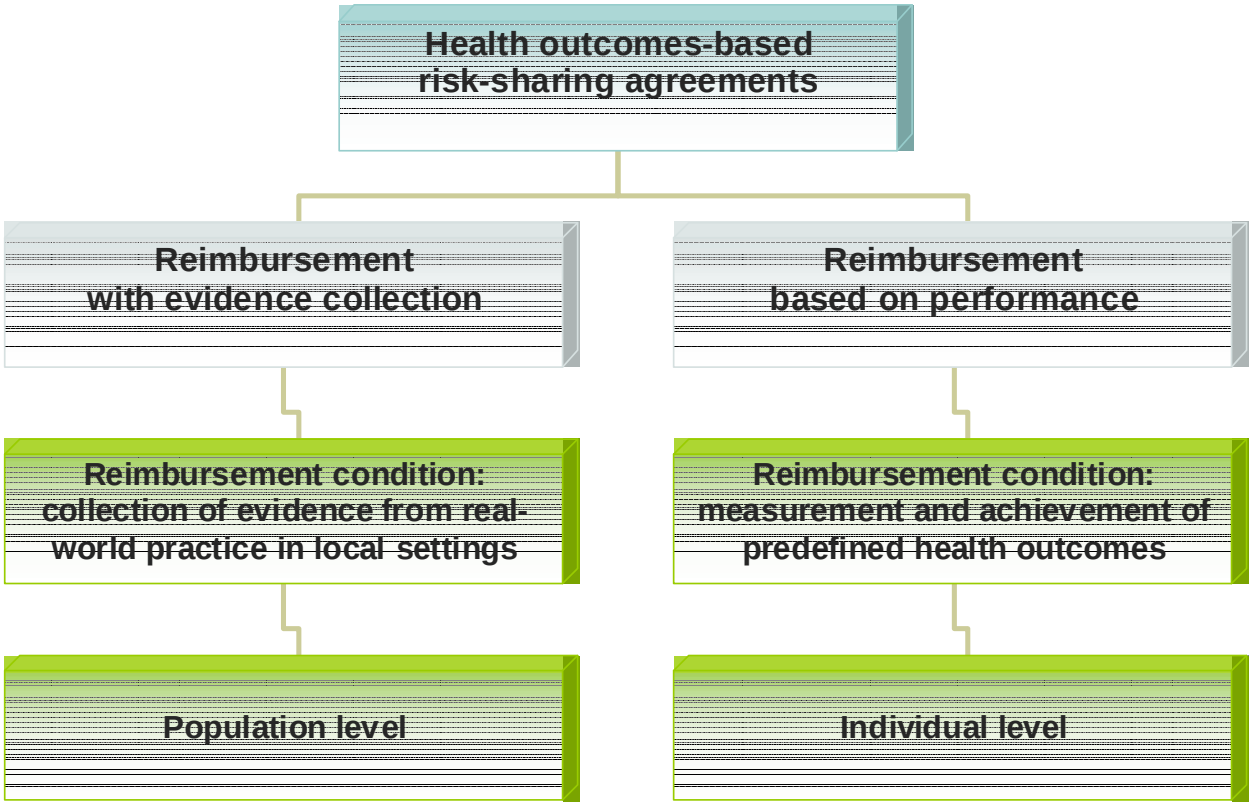

Figure 6. Classification of health coutcomes-based risk-sharing agreements
Adapted from Carlson et al. (2010)[117] & Morel et al. (2013)[33]

Conditional coverage may be further divided in two sub-types: coverage with evidence development and conditional treatment continuation. The first option is applied under the condition of collecting data either as a post-marketing surveillance or in a register.[126] This can be done in two ways – 'only in research' (reimbursed are only patients participating in a study, i.e. new patients are not reimbursed until the study is completed and a final reimbursement decision is taken) or 'only with research' (reimbursed are all patients but they have to consent to participate in the study for data collection, i.e. newly diagnosed patients are reimbursed if they agree to join in). The second sub-type – conditional treatment continuation – is a reimbursement scheme where patient treatment is tied to achieving short-term therapeutic objectives (for instance, lower cholesterol level, tumour response, etc.).[127-129]

The second main category is the so-called performance-linked reimbursement where payment rates are determined by clinical outcomes observed and measured.

Usually the manufacturer commits to certain concessions in case concrete health outcomes are not achieved. Commitment may take the form of price rebate, repayment of expenses already incurred, covering part of treatment costs, etc.[127,130,133,153]

The dividing line between the two approaches is the scope of their application.[153] Conditional coverage with evidence collection is more likely to be applied at population level. The aim is to collect a critical data volume to serve for an objective decision-making about access. In performance-linked reimbursement, higher flexibility at individual level is sought for. Any patient can have access to a therapy as long as it achieves good outcomes for the patient. While the first approach is rather general, the second accounts more for individual patient's specifics and options.

Despite the theoretical differences, many agreements combine elements of both principal categories. For instance, an access scheme could include a conditional treatment continuation and financial guarantees about outcomes. Health otucomes are assessed every therapeutic cycle. If assessment is unsatisfactory, therapy will be terminated and the manufacturer will reimburse expenses. If the outcomes meet the success criteria defined initially, conditional reimbursement will be extended to new cycles and then again outcomes will be assessed.[117]

4.3.5. Coverage with evidence development

Both types of coverage with development scheme have their advantages and disadvantages. In essence, this strategy is a temporary solution setting conditions for information gathering on the basis of which final decision is to be made. Such a final decision may reconfirm the reimbursement status of a health technology, may expand it, limit it or terminate it altogether.[117,126] Temporary reimbursement may be accessible to all patients, including newly diagnosed, or may be restricted to only a sample of patients. In both cases, participation in post-marketing surveillance and registers is a mandatory condition for access to treatments with the health technology in question.[88] This serves several purposes – patients have access to innovative therapies, the payer contains the financial risk, the manufacturer collects evidence in support of its product.[153] This strategy is very popular in countries like the UK, France and Sweden where it is applied to medicinal products as well as to medical devices.[33,117,155-156] Evidence collection is focused on epidemiology and long-term cost-effectiveness of the health technology.

4.3.6. Conditional treatment continuation

The strategy of conditional treatment continuation belongs to conditional coverage category. In this case, reimbursement continues only for patients that have achieved initially defined short-term clinical outcomes.[117,125,153] In this way patients enjoying an effective therapy will continue to have access to it. This strategy addressed the concern when both physicians refrain from interrupting therapy, even if it is not sufficiently effective, i.e. generating costs to the payer with no heath benefits. This relieves the financial burden of health authorities and provides an initial access to treatment to a larger number of patients. A key element here is negotiating indicators for a short-term health outcome which should be objective and equally acceptable to both parties. In Europe this strategy is particularly popular among Italian health authorities.[33,157]

4.3.7. Performance-linked reimbursement

The second category of risk-sharing agreements encompasses the so-called strategies for performance-linked reimbursement. This approach is preferred in cases where the manufacturer feels confident about product efficacy and usefulness.[117,153] Performance-linked agreements include specific guarantees when the product does not meet predetermined therapeutic outcomes. Guarantees may involve reimbursement only for patients with an achieved therapeutic response or manufacturer's commitment to cover expenses of patients with an unsatisfactory clinical outcome.[127,129] This strategy resembles conditional treatment continuation. In fact, both approaches are quite similar. The reason manufacturers prefer the second category of risk-sharing is that gathering evidence is a time- and resource-consuming endeavour, while direct negotiation of guarantees results in savings. However, long-term issues of clinical and cost-effectiveness of therapies are not resolved.[117] As regards to guarantees offered, manufacturers tend to accept covering expenses or making some other types of concessions but not adjusting reimbursement price. The reason is attributed to the existing network for international reference pricing of medicinal products.[129] Overall, this type of strategies are applied to large markets where health authorities can negotiate more favourable concessions. Such schemes are popular in countries like the UK and Germany.[33,128,158]

4.3.8. Mixed schemes

Being aware of the pros and cons of both categories of risk-sharing arrangements, health authorities opt for combinations. Most commonly applied are mechanisms for access entailing individual restrictions and outcome guarantees. [117,128] In this case, the manufacturer agrees to cover all therapy costs exceeding a pre-negotiated limit. This favours the payer for obvious reasons: an innovative therapy is offered at a reasonable price and overuse risk is transferred to the manufacturer. On its part, the manufacturer has an incentive to accept such an arrangement because it secures product reimbursement in a new market and maintains an official reimbursement price for the purposes of international reference pricing.[159] Evidently, setting up limits of the abovementioned type should be substantiated by sound scientific evidence acquired in a real-world environment. Combined risk-sharing agreements contribute particularly to saving on expenditure for diseases with a variable treatment duration, i.e. chronic conditions.

4.3.9. Risk-sharing agreements in rare disease medicinal therapies

Risk-sharing agreements are penetrating also the area of orphan drugs and rare disease medicinal therapies.[33,126-127,130] An European study covering the years 2006 – 2012 reveals a total of 42 such agreements signed in 7 Member States.[33] In itself, however, this is a very negligible figure. Indeed, the majority of these documents are confidential, and information and details about them are not revealed publicly. Yet, it is a fact that risk-sharing agreements exists even in Eastern Europe. This refutes the perception that risk management tools are typically associated with large and wealthy countries. On the contrary, due to the nature of such agreements, they are more favourable to small countries with limited resources because they provide health authorities with higher flexibility in reimbursement and funding of health technologies, including of innovative medicinal therapies.[128]

In England, health authorities have implemented schemes to provide patient access to innovative therapies with a high incremental cost-effectiveness ratio.[26] In the assessment of patient access schemes by NICE, priority is given to unmet health needs, i.e. to patients with no alternative and equally effective treatment options made available.[35,83] In the period 2009 – 2012, English health authorities concluded 33 such

agreements, 8 of them – for orphan drugs. All 8 arrangements were based on non-health-related outcomes (discount, expenditure and application limits per patient).[33]

In Italy, AIFA has been entitled to initiate risk-sharing agreements on innovative medications. A key emphasis is given to uncertainty management by means of web-based registers.[33,127,160-162] AIFA uses these registers for a real-time monitoring and control of the number of patients treated, criteria for therapy initiation, clinical outcomes as well as treatment expenditure. Risk-sharing agreements in Italy can be of two types depending on the financial risk borne – the manufacturer is to repay, in full or in part, expenses made for a treatment demonstrating no therapeutic response. In the period 2006 – 2012, 15 agreements for orphan drugs were concluded.[33]

In Belgium, health authorities have been legally entitled to negotiate risk-sharing agreement for innovative medications with a negative reimbursement status. The arrangement assumes reimbursement of a product for a period of 3 years and a mandatory gathering of evidence. After the term expires, health authorities reconsider their view on product reimbursement.[32,94,98] In the period 2010 – 2012, some 22 agreements were signed, 4 of them – for orphan drugs. Additional clauses dealing with the risk of overspending included expenditure limits (per patient and in total), as well as price rebates.[33]

In the Netherlands, health authorities have applied mechanisms for temporary evidence-based reimbursement of orphan drugs. The therapy itself was reimbursed via state subsidies granted to university medical establishments operating as rare disease expert centres. The manufacturer, on its part, committed to finance post-marketing surveillance and registers so that evidence about clinical cost-effectiveness in real-world settings could be gathered. The duration of these agreements was 4 years. Only after that health authorities evaluated the data collected and took decisions about the final reimbursement status of the medication.[33,96,115]

In Germany, the policy on medications was substantially reorganized in 2011 when an entirely new legal framework was adopted. The experience accumulated thus far is rather poor to enable generalized conclutions.[91] As to innovative medicinal therapies, an early benefit assessment is introduced in order to accelerate patient access to such therapies. The good news here is that orphan drugs are not eligible for such an assessment, i.e. an orphan designation is automatically acknowledged as a clinical value-added of the product. However, when a turnover of € 50 M is reached, the

manufacturer is required to provide real-world data about clinical and cost-effectiveness of the product in order to support health authorities in the final assessment of the orphan drug.[163-166]

4.3.10. Prospects for Bulgaria

For the time being, Bulgaria does not have a legal framework regulating risk-sharing agreements. With respect to medicinal therapies, it is unclear who can enter into such agreements. The National Council on Prices and Reimbursement of Medicinal Products takes the decision about including a product in PDL. The Ministry of Health issues an order to include a disease into the List of diseases for outpatient care under Regulation 38. NHIF pays for these therapies. Clear powers and responsibilities to individual health authority representatives should be delegated in order to succeed in gaining a long-term stability of the public health insurance system.[42,44]

NHIF has put in place some risk control arrangements. They take the form of protocols for prescribing outpatient treatment to rare disease patients. It essence, the approach represents a conditional treatment continuation.[117] In order to continue treatment, some therapeutic indicators set in advance need to be attained. This is a good form of supervision.[128,132] However, it reflects only one side of the coin.

Overspending management approaches need to be sought for, i.e. sharing the financial risk. Currently the entire burden of risk is borne by NHIF.[130] For the purpose, powers and terms for entering into risk-sharing agreements should be legally defined.[85,88] It is important to stress here, that such agreements cannot be drawn up unilaterally since these arrangements are based on a consensus between partners of equal standing. Any attempt to enforce a unilateral decision either by the payer or the manufacturer, is reflected on patient access and therapy quality.[33,79]

Rare diseases and orphan drugs as well as health technology assessment, registers and risk-sharing agreements are relatively new notions to the Bulgarian healthcare system. A future framework for risk-sharing agreements in Bulgaria brings about some issues of a purely practical implementation nature.

High level expertise coupled with European cooperation should be sought for.[3,5,23] It is necessary to distinguish processes of health technology assessment from subsequent decision-making on access to such technologies.[77] The first is a highly specialized activity that is conducted by independent teams in EU Member States while

the second represents, in essence, a political decision and is a prerogative of the health authorities.[26,31,33] Not least, post-marketing surveillance and registers play a central role.[65,117,126,131] Basically, they set the foundation for applying the concepts of health technology assessment and risk-sharing agreement in practice.[77,91-93] Bulgaria and health authorities, in particular, should give serious consideration to making the best out of the expertise and capacity available in the country in order to further develop this strategic information infrastructure and deliver tangible benefits to the healthcare and health insurance system.[94,98]

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1. Bulgarian health authorities demonstrate desire and commitment to improve access to rare disease innovative therapies.

Rare disease patient access to adequate treatment is a consequence of clear, objective and transparent rules put in place for registration, pricing, assessment and reimbursement decision-making. To that end, in the years 2008 – 2014, Bulgaria undertook several political measures aiming to achieve a positive impact, namely by: (Sections 4.1.3-4, 4.2.1, 4.3.1)

- adopting a National Programme for Rare Diseases (2009 – 2013);
- transferring outpatient medicinal therapies from MoH to the mandatory health insurance package;
- amending the regulatory framework on price registration and inclusion of the medicinal products in PDL;
- establishing a National Council on Prices and Reimbursement of Medicinal Products;
- adopting a Regulation on registration of rare diseases and setting up rare disease expert centres and reference networks.

These measures create a sustainable and predictable environment in which the Bulgarian health authorities could meet very effectively European commitments under EC Communication on rare diseases of 2008, Council Recommendation an action in the field of rare disease of 2009 and EU Cross-border healthcare Directive of 2011. In this way Bulgaria demonstrates clearly that it is synchronizing its health policy with global European health priorities under Horizon 2020 Strategic Framework. (Sections 4.1.1-4, 4.2.1, 4.2.4-5, 4.3.1)

The most important outcome, however, is that the health system is better equipped to respond adequately to the health needs of Bulgarian rare disease patients and their families. The entire framework of these political measures is a sign that

Bulgaria is moving in the right direction with respect to rare diseases and this process should continue. (Sections 4.1.3-4, 4.2.4-5, 4.3.1, 4.3.4)

5.2. Access to rare disease therapies in Bulgaria is improving yet remaining limited as compared to other EU Member States.

Out of 72 currently available orphan drugs in EU, 22 are present in PDL Annexes. The remaining 50 orphan drugs, not present in PDL, cannot be reimbursed with public funds and in fact, remain inaccessible to rare disease patients in Bulgaria. In comparison, about 80% of the EU approved orphan drugs are incorporated in the healthcare systems of Member States. For the others, effective regulatory mechanisms are devised and implemented to secure alternative access. (Sections 4.1.1-2, 4.2.3-5, 4.3.3-5)

Accounting for time delay in access to treatment is important since it is an essential factor. In Bulgaria, it takes an average of 43 ± 29.1 months to include a rare disease therapy in PDL after an EU marketing authorization has been issued for the therapy, while in other Member States it takes an average of a year to have a positive reimbursement decision made. In severe, life-threatening and/or debilitating conditions of such rare diseases, timely and adequate access is of crucial importance. (Sections 4.2.4-5, 4.3.2-5)

The issue of access delay and subsequent health implications could be resolved by establishing a specialized state fund designated to ensure therapy of rare disease patients with medicinal products that have been granted an EMA marketing authorization but their reimbursement status in Bulgaria is still pending. This would guarantee timely treatment of patients while avoiding deterioration of patients' condition, and eventual complications which, on their part, could lead to additional health costs at a later stage. Furthermore, health authorities would have time to gather reliable evidence about therapy effectiveness in a real-world setting. (Sections 4.1.2-4, 4.2.4, 4.3.3-4)

5.3. Inclusion of outpatient medicinal therapies for rare diseases in the mandatory health insurance coverage has indeed improved patient access to a timely and adequate treatment.

A large part of problems faced by rare disease patients and their families in Bulgaria stem from insufficient funding and strongly limited access to a timely and adequate treatment.

Back in 2011, these problems were especially acute when rare disease therapies were provided by way of MoH centralized tenders (Figure 7). Since medication volume was fixed, newly diagnosed patients had to wait for up to a year to receive therapy while patients on treatment were frequently placed on a sub-optimal dose. Treatment interruptions due to supply shortage were not uncommon. Hence, apart from loss of quality of life and increased morbidity and mortality, the health system itself suffered economic losses because it paid for an expensive treatment that rendered compromised overall therapeutic effectiveness due to irregular and limited access. The most sticking example to this end was as a paradox: the state covered long-term treatment of children with rare diseases but upon turning 18 years old, the same patient access to treatment was restricted. While long-term therapy produced objective clinical benefits, even few month of interruption or dose limitation that patients faced after coming into the age of 18 led to severe, irreversible health implications wiping away the years of accumulated positive therapeutic outcomes. (Sections 4.1.2, 4.2.3, 4.2.5, 4.3.2)

Discrimination in access to healthcare is the precise term to describe the situation in which rare disease patients and their families were placed before 2011. The Commission for Protection against Discrimination filed several lawsuits and appeals against MoH because of the restricted access to treatment that rare disease patients had to endure in Bulgaria. (Sections 4.1.3-4, 4.2.2, 4.2.4-5, 4.3.2)

After transferring these therapies to NHIF in 2011, the issue of a timely and adequate treatment of rare disease patients has been gradually resolved (Figure 7). Enhanced access has led to a better and more effective treatment, and respectively, to better therapeutic outcomes. Data from rare disease registers existing currently in the country indicate unanimously that life expectancy and quality of life of these patients has improved. This enables the health system to fulfil its mission of granting an accessible and quality healthcare to Bulgarian citizens. (Sections 4.2.3-5, 4.3.4-5)

Furthermore, improved therapy and health outcomes lead to smaller costs per patient, both direct and indirect. The latter are associated with deminished work capacity and early retirement. As indicated by European data, indirect costs borne by society due to rare diseases may significantly exceed direct healthcare expenditure. Not least,

content patients means higher public trust in the Bulgarian healthcare system and satisfaction of its operations. (Sections 4.1.3-4, 4.2.3-5, 4.3.4-5)

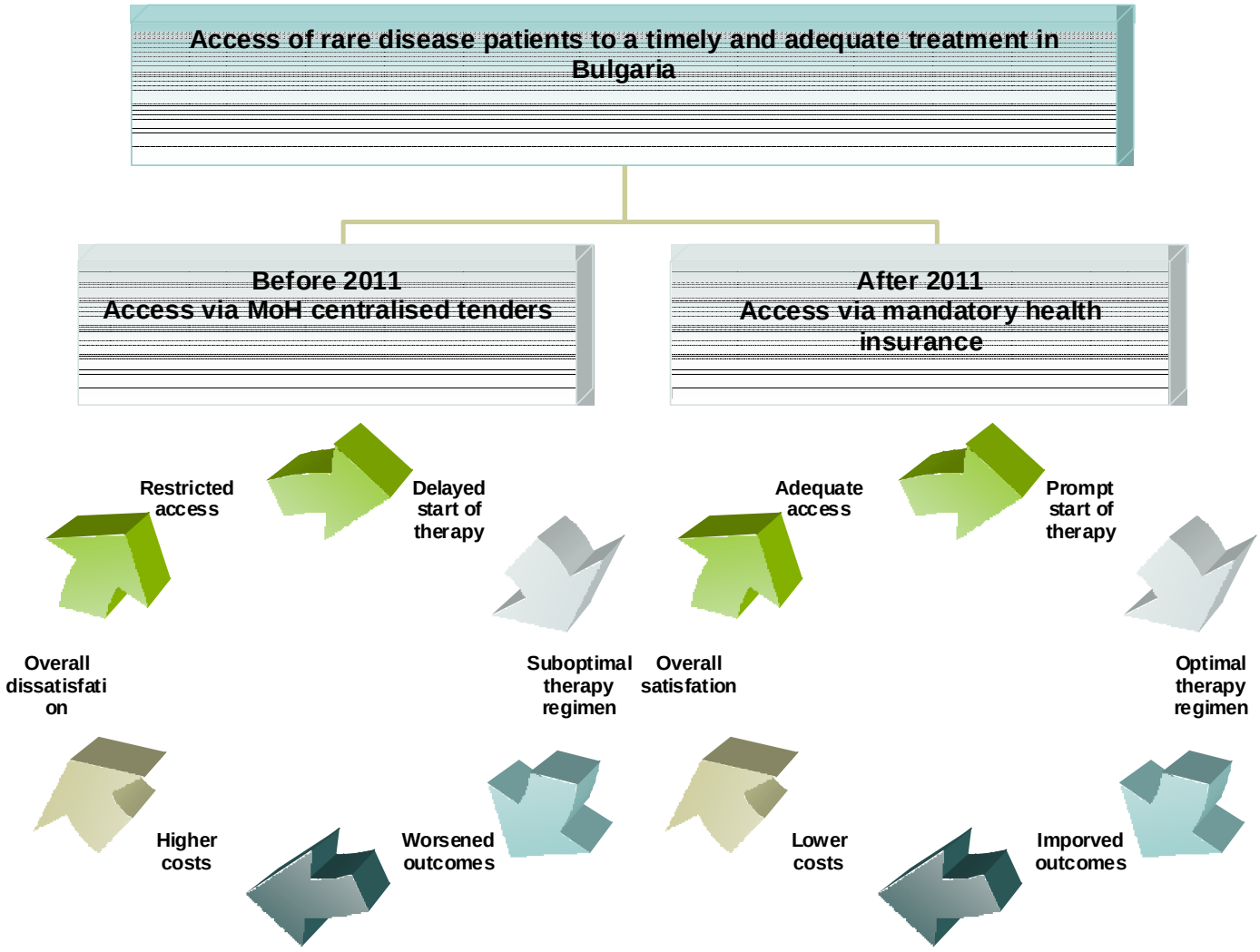

Figure 7. Changes in access to rare disease medicinal therapies in Bulgaria for the period 2011 – 2014

5.4. Budget impact of outpatient medicinal therapies for rare diseases is little and does not pose a risk to stability of the health insurance model in Bulgaria.

The share of expenditure for outpatient rare disease therapies does not exceed 8% of the total NHIF expenditure for medications. For the years 2011 – 2014, the relative share of this budget item has not marked sharp fluctuations. Additions of new rare disease indications to Regulation 38 and new rare disease medicinal products to PDL have not disturbed stability achieved. Absolute NHIF expenditure developments for

outpatient rare disease therapies have remained identical to that of the other expenditure sections in the health insurance budget. (Sections 4.2.1, 4.2.3-5)

A success story for health authorities is the decrease in average expenditure per patient observed for a number of rare diseases following therapies transfer to NHIF. The reduction applies to both expensive treatments, such as for beta thalassemia, Gaucher disease, Fabry disease, Niemann-Pick disease, cystic fibrosis, diabetes insipidus, Turner syndrome and Prader-Willi syndrome, and treatments with a more contained budget impact, such as myasthenia gravis, Wilson disease, other hyperfunctions of pituitary gland and disorders of phosphorus metabolism. Another important finding is that the number of patients treated has also increased. In other words, transfer to NHIF has made these therapies accessible to a larger number of patients at a lower price. (Sections 4.2.2-3)

The current regulatory framework on access to rare disease therapies in Bulgaria is a 'win-win' situation for all stakeholders. Rare disease patients and their families are satisfied since they have prompt and adequate access to an effective treatment and, respectively, enjoy an extended life expectancy and improved quality of life. Health authorities and, in particular, NHIF fulfil their mission by providing timely and quality services to Bulgarian citizens. More people receive treatment, therapeutic outcomes are better, and costs per patient are less. Trust of rare disease patients and their families in Bulgarian healthcare is strengthened because, finally, authorities have found a way to secure coverage of these patients and provide them with quality services. (Sections 4.1.2-3, 4.2.3-5, 4.3.3-4)

5.5. Collecting national epidemiological, clinical and economic data in rare disease registers is of key importance for taking an informed decision about innovative therapies for rare diseases.

Absence of reliable epidemiological, clinical and economic evidence is a serious obstacle to timely and adequate access to innovative therapies for rare diseases in Bulgaria. (Sections 4.1.3-4, 4.3.3)

In the period immediately after acquiring a marketing authorization and actual access to therapies, data volume and level are strongly limited. At EU level, EMA substantiates its drug approval decisions on quality, safety and efficacy of medicinal products. At national level, however, payers require domestic epidemiological, clinical

and economic data about the benefits of a new medication. These encompass comparison with existing treatments, number of patients expected, morbidity dynamics and budget impact of the medicinal product on the health insurance system. Filling the evidence gap is essential to taking an informed decision about access to these therapies. Generation of evidence is a long process with an ultimate aim of gathering relevant national data. (Sections 4.1.3-4, 4.3.2, 4.3.10)

European experience leaves no doubt that epidemiological registers for rare diseases are the best tool to rationalize therapy assessment and reimbursement decision-making processes in this field. National data collected in such registers prove to be more precise and reliable because they reflect local population as well as health system specifics. Bulgarian health authorities should be proactive in encouraging collection of national data on rare diseases. Epidemiological registers should become part of the applicable regulatory framework as a mandatory element of post-marketing surveillance. (Sections 4.1.3-4, 4.2.4-5, 4.3.2, 4.3.5-7)

A possible option for securing access to innovative therapies for rare diseases is to grant access for a defined period of time (for instance, 2-3 years) during which the manufacturer commits to finance setting up and maintaining an epidemiological register for post-marketing surveillance. Register management and scientific support should be entrusted to an independent external body possessing proven experience and expertise in the specific field. Involvement of an independent body would contribute to gathering scientifically sound data and promoting objectivity and transparency. Additionally, registers should be based on nosological units instead of medicinal products. This would facilitate assessment and comparison of clinical and economic effectiveness of therapies. Equipped with such information, health authorities would be able to evaluate benefits and costs of an innovative therapy and take an informed decision regarding access to it. (Sections 4.1.2, 4.2.4-5, 4.3.3-10)

5.6. Implementation of risk-sharing agreements will optimize planning and management of public expenditure for rare disease therapies in Bulgaria.

The Bulgarian health system has limited resources and any unplanned rise in number of patients treated and/or costs per patient may lead to a substantial deficit. This finding applies to any NHIF budget section. NHIF employs conditional reimbursement of rare disease therapies, i.e. protocols for prescribing treatment and

treatment continuation when defined therapeutic outcomes are achieved. In theory this model works since it guarantees that patient responding favourably to the therapy will remain on the treatment. However, a significant setback of this tool is the absence of an effective mechanism to manage overspending risk. Healthcare expenditure, including for rare diseases, will continue its upward trend for various reasons, some of them quite objective, such as population aging, degraded health status and increased prevalence of chronic non-contagious diseases. (Sections 4.2.4-5, 4.3.5-10)

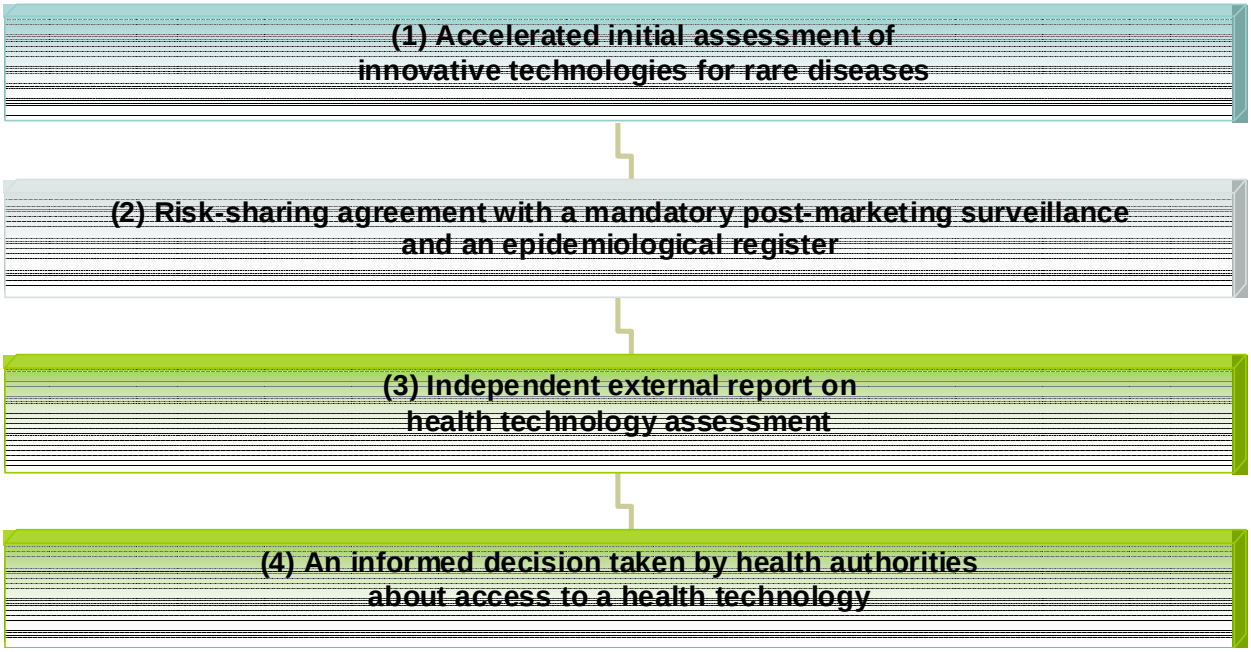

Figure 8. Proposal for a model of sustainable access to rare disease therapies in Bulgaria

NHIF needs tools to tackle successfully overspending risk. Experience in other Member States shows that risk-sharing agreements could be very useful to that end. Implementation of these mechanisms starts with establishing a relevant legal foundation that will enable an accelerated and implicit initial assessment of innovative technologies for rare diseases. Health authorities should act proactively when EMA approves such therapies in order to grant timely and adequate access to treatment of rare disease patients. (Sections 4.2.5, 4.3.1, 4.3.3-10)

Risk-sharing agreements with a mandatory condition of having a register to record post-marketing surveillance data would allow patients to start therapy at an early stage and avoid clinical complications incurring additional health costs. Health authorities would have time to acquire sufficient data about the actual efficacy of the product and proceed with an informed decision-making at a later stage. This serves a dual purpose regarding access: on the one hand, it would be made more transparent, and on the other hand, it would be scientifically and practically driven.

To a considerable extent, the trust in the health system and the satisfaction of its operations depend on the mechanisms applied in decisions for access to treatment. When decisions are well-argued, when they are formulated on the grounds of a transparent procedure and clear criteria, they are accepted by all shareholders, and the health system would operate on an equitable basis in conformity with public attitudes and patients needs, and therapeutic outcomes would match healthcare expenditure made. This is how health authorities may contribute to increasing efficiency and long-term sustainability of the health insurance system. (Sections 4.1.2-4, 4.2.4-5, 4.3.3-10)

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APPENDIX 1

Dear Respondent,

The **Institute for Rare Diseases in Bulgaria** is attempting to explore **the current best practices regarding the registration, pricing and reimbursement of the medicinal products for rare diseases (orphan drugs) in Europe**. We hope to measure the progress in this field, identify best practices, and strengthen the bond among rare disease and orphan drug stakeholders.

Please complete the enclosed questionnaire, which will take 15 minutes. Your candid and thoughtful replies will help our study. Your responses and any comments will be treated with utmost confidentiality. After the results are tabulated and compiled, we will issue a report.

Thank you for your help.

Sincerely,

Georgi Iskrov
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SURVEY METHODOLOGY

Before completing the survey, please consult with the definitions, and inclusion/exclusion criteria used.

Definition

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 defines that a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) 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

(b) 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.

Inclusion criteria

The present study is focusing on **medicinal products for rare diseases**:

(a) with **a European Community marketing authorisation** under **the centralised procedure of EMA**, that is issued **until the end of 2013**;

and

(b) with **an orphan designation** under Regulation (EC) No 141/2000, or with **an exclusive indication for prevention, diagnosis and treatment of rare diseases**.

Exclusion criterion

(a) The present study **excludes** medicinal products for rare diseases with an ICD-10 code of C00-D48 (**all forms of cancer**).

There are 52 questions in this survey.

RESPONDENT PROFILE

1. Please enter your name:

2. Please enter your country:

3. Please enter your affiliation:

4. Is your affiliate organisation involved in one or more of the following activities? Check any that apply.

Registration of orphan drugs	
Pricing of orphan drugs	
Assessment and appraisal of orphan drugs	
Reimbursement decision-making for orphan drugs	
Access to non-registered orphan drugs	
Access to non-reimbursed orphan drugs	
None of the listed above	
Other (please specify)	

5. Please describe in brief your relevant experience in the activities indicated above:

REGISTRATION OF MEDICINAL PRODUCTS FOR RARE DISEASES

6. Are orphan drugs, which are marketed under the centralised procedure of EMA, automatically registered in your country/region/province or they have to undergo a formal registration, initiated by a representative of the market authorisation holder? Choose one of the following answers.

Orphan drugs are automatically registered and no further actions by the market authorisation holder are required	
Orphan drugs are automatically registered, but a formal registration process has to be initiated by a representative of the market authorisation holder	
Other (please specify)	

7. Which institution is chiefly responsible for the registration of orphan drugs in your country/region/province?

Institution:	

8. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

9. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

PRICING OF MEDICINAL PRODUCTS FOR RARE DISEASES

10. Which institution is chiefly responsible for the pricing (setting the publicly declared price before any confidential deals) of orphan drugs in your country/region/province?

Institution:	

11. Are orphan drugs object of general or special drug pricing policies in your country/region/province? Choose one of the following answers.

General drug pricing policies	
Special registration and pricing policies for orphan drugs	
Other (please specify)	

12. Which types of drug pricing policies for orphan drugs are enacted in your country/region/province? Check any that apply.

Direct price control (setting of a fixed maximum price of a medicinal product, statutory pricing, price negotiations, public procurement, etc.)	
Free pricing	
International price comparison (or external reference pricing)	
Profit controls (rate of return regulation)	
Internal reference pricing	
Other (please specify)	

13. Are healthcare providers (e.g., centres of expertise, hospitals, etc.) allowed to additionally negotiate the officially set price of orphan drugs (e.g., negotiations for a discount, organisation of public tenders, etc.)? Choose one of the following answers.

Yes	
No	
Other (please specify)	

14. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

15. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

ASSESSMENT AND APPRAISAL OF MEDICINAL PRODUCTS FOR RARE DISEASES

16. Are orphan drugs object of general or special drug assessment and appraisal policies in your country/region/province? Choose one of the following answers.

General drug assessment and appraisal policies	
Special assessment and appraisal policies for orphan drugs	
Other (please specify)	

17. Which institution is chiefly responsible for assessment and appraisal of orphan drugs in your country/region/province?

Institution:	

18. Does the assessment and appraisal institution in your country/region/province directly accept EMA's assessment of the clinical benefits and effectiveness of orphan drugs? Choose one of the following answers.

Yes	
No	
Other (please specify)	

19. Does the assessment and appraisal institution in your country/region/province require orphan drugs to provide additional (supporting) data on their clinical benefits and effectiveness? Choose one of the following answers.

Yes	
No	
Other (please specify)	

20. Which institution is chiefly responsible for the reimbursement decision-making of orphan drugs in your country/region/province?

Institution:	

21. Which criteria/considerations are observed in this process? Check any that apply.

Clinical effectiveness	
Cost-effectiveness	
Budget impact	
Societal considerations (e.g., solidarity, unmet health needs)	
Other (please specify)	

22. Do the EMA's orphan designation and market authorisation mean an automatic positive reimbursement decision by the relevant institution in your country/region/province,

without an explicit assessment and appraisal process at national level? Choose one of the following answers.

Yes	
No	
Other (please specify)	

23. Please indicate the date when a positive decision on reimbursement with public funds was made in your country/region/province for the following drugs for rare diseases:

Drug	Indication	Date of positive reimbursement decision
ELAPRASE (Idursulfase)	Mucopolysaccharidosis type II	
EXJADE (Deferasirox)	Beta thalassaemia major	
GLYBERA (Alipogene tiparvovec)	Familial lipoprotein lipase deficiency	
KUVAN (Sapropterin dihydrochloride)	Phenylketonuria Tetrahydrobiopterin deficiency	
VYNDAQEL (Tafamidis)	Transthyretin amyloidosis	
VOLIBRIS (Ambrisentan)	Pulmonary arterial hypertension	
CEREZYME (Imiglucerase)	Gaucher disease	
SOMAVERT (Pegvisomant)	Acromegaly	
KOGENATE BAYER (Octocog alpha)	Haemophilia A (congenital factor VIII deficiency)	

24. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

25. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

REIMBURSEMENT OF MEDICINAL PRODUCTS FOR RARE DISEASES

26. In case of a positive decision on reimbursement with public funds, orphan medicinal therapy is funded by whom in your country/region/province? Check any that apply.

National health authorities (e.g., through the budget of the Ministry of Health)	
Regional and local health authorities (e.g., through the budget of regional and local health authorities)	
Public health insurance funds	
Private health insurance funds	
Donators (e.g., charity funds)	
Public funded hospitals	
Other (please specify)	

27. Within the body which is funding orphan drug therapies in your/region/province, orphan drugs are funded by what type of budget? Choose one of the following answers.

General budget that is funding all kind medicinal therapies	
Separate budget that is funding only orphan medicinal therapies (including orphan drugs for oncological diseases)	
Separate budget that is funding only orphan medicinal therapies (excluding orphan drugs for oncological diseases)	
Other (please specify)	

28. Are patients required to make co-payments for orphan drugs in your country/region/province? Choose one of the following answers.

Yes	
No	
Other (please specify)	

29. If yes, what is the approximate co-payment rate in your country/region/province?

Approximate co-payment rate:	

30. Apart from the reimbursement from public funds, are there additional financial resources for orphan drugs in your country/region/province (e.g, special fund for orphan drugs, charity)? Choose one of the following answers.

Yes	
No	
Other (please specify)	

31. Are there official lists (e.g., public database) with orphan drugs, which are reimbursed by public funds in your country/region/province? Choose one of the following answers.

Yes	
No	
Other (please specify)	

32. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

33. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

ACCESS TO NON-REGISTERED ORPHAN DRUGS

34. Are there legal ways for individual patients to access non-registered orphan drugs in your country/region/province (e.g., compassionate use, expanded access programme, named patient programmes, off-label use, etc)? Choose one of the following answers.

Yes	
No	
Other (please specify)	

35. If yes, which legal ways for individual patients to access non-registered orphan drugs are available in your country/region/province? Check any that apply.

Compassionate use (the use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions; this helps to make medicines that are still under development available to patients)	
Expanded access programmes	
Named patient programmes	
Off-label use	
Other (please specify)	

36. If yes, therapy with these drugs is funded by whom? Check any that apply.

National health authorities (e.g., through the budget of the Ministry of Health)	
Regional and local health authorities (e.g., through the budget of regional and local health authorities)	
Public health insurance funds	
Private health insurance funds	
Donators (e.g., charity funds)	
Public funded hospitals	
Other (please specify)	

37. Are patients required to make co-payments in this case? Choose one of the following answers.

Yes	
No	
Other (please specify)	

38. If yes, what is the approximate co-payment rate?

Approximate co-payment rate:	

39. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

40. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

ACCESS TO NON-REIMBURSED ORPHAN DRUGS

41. Are there alternative ways for individual patients to access registered but non-reimbursed orphan drugs in your country/region/province (e.g., risk-sharing and pay-for-performance arrangements)? Choose one of the following answers.

Yes	
No	
Other (please specify)	

42. If yes, which legal ways for individual patients to access non-reimbursed orphan drugs are available in your country/region/province? Check any that apply.

Risk-sharing arrangements	
Pay-for-performance arrangements	
Other (please specify)	

43. If yes, therapy with these drugs is funded by whom? Check any that apply.

National health authorities (e.g., through the budget of the Ministry of Health)	
Regional and local health authorities (e.g., through the budget of regional and local health authorities)	
Public health insurance funds	
Private health insurance funds	
Donators (e.g., charity funds)	
Public funded hospitals	
Other (please specify)	

44. Are patients required to make co-payments in this case? Choose one of the following answers.

Yes	
No	
Other (please specify)	

45. If yes, what is the approximate co-payment rate?

Approximate co-payment rate:	

46. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

47. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

COSTS FOR MEDICINAL PRODUCTS FOR RARE DISEASES

48. Are there budget constraints for the reimbursement of orphan drugs in your country/region/province (e.g., fixed overall budget for orphan drugs, etc.)? Choose one of the following answers.

Yes	
No	
Other (please specify)	

49. If yes, which types of budget constraints are applied to orphan drugs? Check any that apply.

Fixed overall budget for drugs	
Fixed overall budget for orphan drugs	
Other (please specify)	

50. If available, please indicate the total amount of public funds spent on orphan drugs in your country/region/province?

Total public budget for health in your country/region/province	
Approximate total amount of public budget for health spent on drugs	
Approximate total amount of public budget for health spent on orphan drugs (including orphan drugs for oncological diseases)	
Approximate total amount of public budget for health spent on orphan drugs (excluding orphan drugs for oncological diseases)	
Reference year	

51. Please use this field to make any comments and/or clarifications regarding this section, as well as the input you have provided.

52. Please use this field to provide any references (official documents, scientific publications, grey literature, etc.) that you consider relevant for the topics discussed.

Thank you!

After the results are tabulated and analyzed, we will issue a summary report. We will keep you informed on the progress of this survey.

APPENDIX 2

NHIF TOTAL EXPENDITURE FOR 2011 FOR MEDICINAL THERAPIES

Indicator	Amount laid down pursuant to the Law on NHIF Budget for 2011 (BGN thousand)	Actual amount spent for 2011 (BGN thousand)*
Health insurance payments for home treatment, medical devices and diet food for special medical purposes	391 000	524 471
NHIF total expenditure for 2011 for medicinal therapies	**391 000**	**524 471**

** Data have been formally received from NHIF in accordance with the Law on Access to Public Information.*

APPENDIX 3

NHIF TOTAL EXPENDITURE FOR 2012 FOR MEDICINAL THERAPIES

Indicator	Amount laid down pursuant to the Law on NHIF Budget for 2012 (BGN thousand)	Actual amount spent for 2012 (BGN thousand)*
Health insurance payments for home treatment, medical devices and diet food for special medical purposes	495 525	484 109
Health insurance payments for inpatient medical care (medicinal therapy)	57 584	116 261
NHIF total expenditure for 2012 for medicinal therapies	**553 109**	**600 370**

** Data have been formally received from NHIF in accordance with the Law on Access to Public Information.*

APPENDIX 4

NHIF TOTAL EXPENDITURE FOR 2013 FOR MEDICINAL THERAPIES

Indicator	Amount laid down pursuant to the Law on NHIF Budget for 2013 (BGN thousand)	Actual amount spent for 2013 (BGN thousand)*
Health insurance payments for home treatment and diet food for special medical purposes	497 000	544 295
Health insurance payments for medical devices	70 000	79 171
Health insurance payments for inpatient medical care (medicinal therapy)	90 000	162 050
NHIF total expenditure for 2013 for medicinal therapies	**657 000**	**785 516**

** Data have been formally received from NHIF in accordance with the Law on Access to Public Information.*

APPENDIX 5

NHIF TOTAL EXPENDITURE FOR 2014 FOR MEDICINAL THERAPIES

Indicator	Amount laid down pursuant to the Law on NHIF Budget for 2014 (BGN thousand)	Actual amount spent for 2014 (BGN thousand)*
Health insurance payments for home treatment and diet food for special medical purposes	527 000	332 708
Health insurance payments for medical devices	82 000	46 562
Health insurance payments for inpatient medical care (medicinal therapy)	145 000	98 141
NHIF total expenditure for 2014 for medicinal therapies	**754 000**	**477 411**

** Data have been formally received from NHIF in accordance with the Law on Access to Public Information.*

Introducing and applying the concept of **health technology assessment** in Bulgaria would allow for more transparency, objectivity and efficiency in the health system. Availability of capacity and settings for conducting rare disease-specialised health technology assessment is crucial for the ultimate success of all policies and strategies for rare diseases in the country. The most important outcome is the extended life expectancy and improved quality of life for patients with rare diseases. These two measures directly depend on the timely access to advanced diagnostic and therapeutic health technologies.

Since its establishment in 2003, **the Bulgarian Association for Promotion of Education and Science**, BAPES (a non-government non-profit organisation) has been working to raise the awareness of rare diseases among the medical community and the society as whole in Bulgaria.

BAPES has consecutively launched **the Information Centre for Rare Diseases and Orphan Drugs** (2004) and **the "RareDis" Medical Centre** (2009), as project activities that are explicitly designed to meet the rare disease patients' needs for reliable information and for opportunities for adequate diagnosis, treatment, follow-up and rehabilitation. BAPES started the **Centre for Analyses and Health Technology Assessment and Analysis** in 2013 to take over the dynamic area of health technology assessment, particularly in field of rare diseases and orphan drugs.