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PHARMACOEPIDEMIOLOGIC AND PHARMACOECONOMIC LATVIAN STUDY OF RARE DISEASES AND ORPHAN DRUGS

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The Doctoral Thesis is available in the RSU library and at RSU webpage: www.rsu.lv.

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ABBREVIATIONS

AE	adverse events
BMC	Latvian Biomedical Research and Study Center
CCUH	Children's Clinical University Hospital
CDPC	Center for Disease Prevention and Control
CF	cystic fibrosis
CI	confidence interval
CLL	chronic lymphocytic leukaemia
COMP	Committee for Orphan Medicinal Products
CT	clinical trial
DFS	disease-free survival
DFSP	dermatofibrosarcoma protuberans
EEA	European Economic Area
EMA	European Medicines Agency
ERT	enzyme replacement therapy
EU	European Union
EUCERD	European Union Committee of Experts on Rare Diseases
EudraCT	European clinical trials database
EUR	Euro
EURORDIS	European Organization for Rare Diseases
GBP	British pound sterling
GDP	gross domestic product
GIST	gastrointestinal stromal tumours
HES	hypereosinophilic syndrome
HSCT	haematopoietic stem cell transplantation
HTA	health technology assessment
IMP	investigational medicinal product

IMS	Intercontinental Medical Statistics
INN	international nonproprietary name
ISO	International Organization for Standardization
ITP	immune (idiopathic) thrombocytopenic purpura
LV	Latvia
LVL	Latvian Lat
MAH	marketing authorization holder
MDR-TB	multidrug-resistant tuberculosis
MDS/MPD	myelodysplastic/myeloproliferative diseases
MEN	multiple endocrine neoplasia
MoH	Ministry of Health
MPS	mucopolysaccharidosis
NHS	National Health Service
NSAID	non-steroidal anti-inflammatory drug
OS	overall survival
PAH	pulmonary arterial hypertension
PFS	progression-free survival
Ph+ ALL	Philadelphia chromosome positive acute lymphoblastic leukaemia
Ph+ CML	Philadelphia chromosome positive chronic myelogenous leukemia
PK	pharmacokinetics
PKU	phenylketonuria
pNET	pancreatic neuroendocrine tumours
PSCUH	Pauls Stradins Clinical University Hospital
QoL	quality of life
RCC	renal cell carcinoma
RCT	randomized controlled trial
RECUH	Riga East Clinical University Hospital
RSU	Riga Stradins University

SAM	State Agency of Medicines
SCC	sputum culture conversion
SLL	small lymphocytic lymphoma
SPC	summary of product characteristics
T-ALL	T-cell acute lymphoblastic leukaemia
T-LBL	T-cell lymphoblastic lymphoma
TSC	tuberous sclerosis complex
US	United States
USD	United States Dollar

INTRODUCTION

Relevance of the study

Rare diseases are life-threatening or chronically debilitating conditions of different origin. The majority of them are genetic disorders, others being rare cancers, autoimmune, toxic and infectious diseases (Communication from the Commission, 2008). It is estimated that between five and eight thousand different rare conditions exist, affecting 6–8 % of the population, concluding that about 30 million people are suffering from rare disorders in the European Union (EU). More than ten years have passed since Latvia became a Member State of the EU. Since then the EU laws and regulations, including those related to rare diseases, have been applied to Latvian legislative system. According to the EU regulations disease is considered as rare if it affects not more than five in ten thousand people (Regulation (EC) No. 141/2000, 2000). Most patients suffer from even rarer disorders affecting one person in 100 000 or less (Council Recommendation, 2009), and it could be very difficult to diagnose and manage these conditions in relatively small populations. Generally there is a limited public awareness of the rare diseases. The national healthcare services for these disorders differ significantly among the EU countries, resulting in unequal access to diagnostics and treatment. Considering all the above mentioned European Council recommended Member States to establish and implement national plans for rare diseases by the end of 2013 (Council Recommendation, 2009).

Development of medicinal products intended for the treatment, diagnosis or prevention of rare diseases (orphan drugs) can be very challenging due to distinct rare disease features, such as low event rates, inadequate understanding of disease natural course, and a lack of previous clinical trials (Kakkis et al., 2015). The most obvious challenge in rare disease trials is the recruitment of the right patients in adequate numbers (Buckley, 2008; Gagne et al., 2014; Griggs et

al., 2009), therefore multicenter and multinational collaboration is often required. Randomized controlled trials (RCT) are available for approximately 60 % of orphan drugs authorized in the EU (Joppi, Bertele and Garattini, 2009, 2013; Kanters et al., 2013; Picavet et al., 2013; Winstone et al., 2015). Most of the European Medicines Agency (EMA) approved orphan drugs demonstrated moderate overall quality of clinical evidence (Onakpoya et al., 2015; Winstone et al., 2015). The majority of the drugs were tested in trials involving fewer than 200 patients and lasting less than two years (Joppi, Bertele and Garattini, 2013). Nearly half of the studies applied some type of blinding (Picavet et al., 2013) and used placebo as a comparator (Joppi, Bertele and Garattini, 2013). Duration of orphan drug trials is often too short in relation to the natural history of the disease (Dupont and Van Wilder, 2011; Joppi, Bertele and Garattini, 2009, 2013). Dose finding studies and the use of active comparators are frequently lacking. Nevertheless, clinical studies can allow rare disease patients access to investigational drugs, while the quality of data from these studies may affect reimbursement decisions and further market access of rare disease therapies (Winstone et al., 2015).

The EU offers a number of incentives to promote the development of orphan medicines since, under normal market conditions, pharmaceutical companies have little interest in developing products intended for small numbers of patients (Binns and Driscoll, 2000). The incentives include assistance in drug development, reduced fees for marketing authorization, and protection from market competition once the drug is authorized (10 years of marketing exclusivity) (Regulation (EC) No. 141/2000, 2000). Orphan designation refers to awarding of orphan status to a drug, but marketing authorization refers to the approval to market the product. Applications for orphan designation are examined by the EMA Committee for Orphan Medicinal Products (COMP), which adopts an opinion that is forwarded to the European Commission, which

afterwards decides whether to grant an orphan designation for the drug in question. Then pharmaceutical company submits a single marketing authorization application to the EMA under the centralized procedure. Once granted by the European Commission, a centralized marketing authorization for orphan medicinal product is valid in all the EU states. The EMA supports the approval of medicines that address unmet medical needs (including orphan drugs), on the basis of less comprehensive clinical data than normally required, through the conditional marketing authorization or through the marketing authorization under exceptional circumstances. The EMA has also adopted the guideline on clinical trials in small populations (EMA, 2006). While many medicines may have received an orphan designation, few have received a marketing authorization. By the end of 2014, there were more than a thousand positive opinions on orphan designation, but less than 80 orphan drugs with active marketing authorization in the EU (some of them are intended for the same condition) (EMA, 2015; European Commission, 2015). Most of them are indicated for treatment of oncological conditions (Denis et al., 2010b; Iskrov and Stefanov, 2014; Meekings, Williams and Arrowsmith, 2012; Orofino et al., 2010), followed by metabolic and endocrine diseases (including lysosomal storage diseases) and cardiovascular disorders (particularly pulmonary arterial hypertension).

Whereas decisions surrounding orphan designation and marketing authorization of orphan drugs are taken at the EU level, decisions governing pricing and reimbursement of orphan drugs are a member state responsibility. An orphan drug is generally considered to be available when it is market authorized and priced. To be accessible, however, it needs to be reimbursed by public fund. Factors, such as costs of research and development, marketing exclusivity, lack of alternative therapies, disease severity, and small market size can affect orphan drug prices (Drummond et al., 2007). Moreover, orphan drugs for treatment of

diseases with lower prevalence generally have higher costs than drugs indicated to treat more common conditions (De Varax, Letellier and Börtlein, 2004; Orofino et al., 2010). Especially drugs for ultra-orphan diseases (Onakpoya et al., 2015), with a prevalence of less than 1 per 50 000 persons, are highly expensive. In fact, orphan designated drugs tend to have higher prices than non-designated drugs for rare diseases (Picavet et al., 2011). Standard cost-effectiveness criteria are often not applicable to orphan drugs (Denis et al., 2010a; Drummond et al., 2007), considering the high costs of these medicines and often modest health gains. Budget impact of orphan drugs is growing, which puts pressure on decision makers. Given current fiscal constraints and financial uncertainty around orphan drugs, health authorities are increasingly concerned about the growth in orphan drug expenditure and its impact on their limited budgets. On the one hand, budget impact for an individual orphan drug is usually small (Hutchings et al., 2014; Kanters, Steenhoek and Hakkaart, 2014), due to the limited numbers of patients. The majority of orphan drugs have relatively low sales (Hutchings et al., 2014), except few high-cost orphan drugs. Though, budget impact for orphan drugs altogether might be considerable (Kanters, Steenhoek and Hakkaart, 2014; Schey, Milanova and Hutchings, 2011).

Orphan drug availability, accessibility, pricing and reimbursement policies differ between European countries (Denis et al., 2010a; Iskrov, Miteva-Katrandzhieva and Stefanov, 2012; Pavlović et al., 2012). Some countries consider the budget impact and cost-effectiveness of orphan drugs in their reimbursement decisions. For example, in France, Italy, the Netherlands, the UK, and Serbia reimbursement is based on both, cost-effectiveness and budget impact. In contrast, Belgium and Bulgaria do not consider the cost-effectiveness, while the budget impact analysis is not required in Sweden. It has been shown that a low gross domestic product (GDP) value and availability of a formal health technology assessment (HTA) organization have negative influence on orphan

drug market uptake (Picavet et al., 2012). Budget impact analyses conducted so far focused predominantly on the old EU countries with a high GDP (markets with high drug expenditures) or Europe as a whole (De Varax, Letellier and Börtlein, 2004; Denis et al., 2009, 2010b; Hutchings et al., 2014; Kanters, Steenhoek and Hakkaart, 2014; Orofino et al., 2010; Schey, Milanova and Hutchings, 2011; Schlander, Adarkwah and Gandjour, 2015). In contrast, Latvian study could provide an insight on the situation in a small Eastern European country with a low GDP.

Aim of the study

The aim of the study was to determine situation in the field of rare diseases in Latvia, assess the impact of orphan drugs on the state budget and compare the findings with data from other European countries.

Objectives of the study

1) To assess the national policy in the field of rare diseases, diagnostic and treatment options for rare diseases, as well as activities related to rare disease patient registers and patient organizations in Latvia.
2) To evaluate the characteristics of clinical trials in rare diseases conducted in Latvia and compare them with clinical trials in more common conditions.
3) To assess orphan drugs associated with surgery as a specific therapeutic area.
4) To analyze availability and accessibility of the EU authorized orphan drugs in Latvia.
5) To analyze budget impact of orphan drugs in Latvia and to compare the findings with data from other European countries.

Hypotheses of the study

1) In Latvian healthcare system, the extent of rare disease recognition, inventory, prevention, diagnosis, treatment, rehabilitation, and research is not sufficient.
2) Latvia is a country with limited availability and accessibility of orphan drugs.
3) Budget impact of orphan drugs in Latvia is small in comparison with other European countries.

Novelty of the study

Orphan diseases have been recognized as a priority area for the European Community action in the public health system, though there are significant differences in the national healthcare services for rare disease patients among the EU States. Studies conducted in the field of rare diseases and orphan drugs so far focused predominantly on the old EU countries or Europe as a whole. There is a lack of such studies in Eastern European countries, including the Baltic States. In the current study, a comprehensive insight on the situation in the field of rare diseases in Latvia is provided for the first time. In addition, the impact of orphan drugs on the state budget is assessed and the findings are compared with data from other European countries.

Individual contribution

Under the scientific supervision, the author of the current study developed the methodology of the study, performed a literature review, collected and analyzed the data, interpreted the results, and wrote the doctoral thesis. In

addition, the author participated in meetings of the Working group on "The development of the action plan for organization of health care for rare disease patients" held by the Ministry of Health of the Republic of Latvia.

Structure and volume of the study

The doctoral thesis is written in Latvian. It has summaries in Latvian and English. The thesis is structured as a thematically related set of scientific publications, which includes the following publications:

1) Logviss, K., Krievins, D. and Purvina, S. 2014. Rare diseases and orphan drugs: Latvian story. *Orphanet J Rare Dis*. 9:147, which partly covers the publication: Logviss, K., Krieviņš, D. un Purviņa, S. 2011. Retās slimības un orfānzāles Latvijā. *RSU Zinātniskie raksti*. 1, 313–317;
2) Logviss, K., Krievins, D. and Purvina, S. 2016. Impact of orphan drugs on Latvian budget. *Orphanet J Rare Dis*. 11:59, which partly covers the publication in the Proceedings of the 4th International Interdisciplinary Scientific Conference Society, Health, Welfare: Logviss, K., Krievins, D. and Purvina, S. 2014. Trends in individual reimbursement of orphan drugs in Latvia in 2008–2011. *SHS Web of Conferences*. 10:00021;
3) Logviss, K., Krievins, D. and Purvina, S. 2018. Characteristics of clinical trials in rare vs. common diseases: A register-based Latvian study. *PLoS One*. 13(4):e0194494;
4) Logviss, K., Krievins, D. and Purvina, S. 2013. Orphan Drugs in Surgery. *Acta Chirurgica Latviensis*. 13(1), 57–62.

The doctoral thesis consists of the following parts: introduction, literature review, materials and methods, results, discussion, conclusions, recommendations, list of references, and appendices. Volume of the thesis – 105

pages, including 13 tables, 12 figures, and 3 appendices. The list of references contains 92 references (85 references in the summary of the thesis).

1. MATERIALS AND METHODS

1.1. Assessment of the situation in the field of rare diseases in Latvia

The following sources of information were used to evaluate situation in the field of rare diseases in Latvia: National Plan for Rare Diseases, EUCERD (European Union Committee of Experts on Rare Diseases) 2012, 2013, and 2014 Reports on the State of the Art of Rare Disease Activities in Europe, Statistics of the Center for Disease Prevention and Control, Latvian Orphanet data, and laws and regulations of the Cabinet of Ministers.

1.2. Analysis of clinical trials in rare diseases

1.2.1. EU Clinical Trials Register

The EU Clinical Trials Register (*clinicaltrialsregister.eu*) was used to identify clinical trials related to rare diseases and to compose a control group of clinical trials in non-rare diseases for further comparison of the trial characteristics. The register contains information on interventional clinical trials on medicines conducted in the EU, or the European Economic Area (EEA), which started after 1 May 2004. The present study was performed in May 2016, covering a period of 12 years. The EU Clinical Trials Register provides the public with information held in the EU clinical trials database (*EudraCT*). The *EudraCT* database is maintained by the EMA and used by the national competent authorities to enter clinical trial data, originally provided by the sponsor, and to support supervision of clinical trials.

1.2.2. Search strategy

Advanced search tools (filters) were used to restrict the search to clinical trials related to rare diseases that were conducted in Latvia. The search filters used included: "Country – Latvia", "Rare disease", and "Investigational medicinal product (IMP) with orphan designation in the indication". A total of 51 clinical trials with a unique *EudraCT* number, which identifies the trial throughout its lifespan, were identified. The detailed trial protocol-related data were accessed through the Organization for Standardization (ISO) country code for Latvia (LV). Data displayed for some clinical trials were incomplete or contained inconsistencies. For the missing information of such trials, we used data provided by other EEA countries (via the *clinicaltrialsregister.eu*) and/ or *ClinicalTrials.gov* (a clinical trials database maintained by the US National Library of Medicine at the National Institutes of Health). The following characteristics of the trials were analyzed: primary endpoints, randomization, masking, comparators, estimated trial enrollment and duration.

1.2.3. Control group

For the control group of clinical trials in non-rare diseases, 376 unique clinical studies in common conditions conducted in Latvia were initially classified by therapeutic areas and trial phases. Then, 102 clinical trials were randomly chosen to compose the control group. Ratio of the control group clinical trials to rare disease clinical trials was 2:1. Proportions of therapeutic areas and trial phases were maintained between the two groups for comparability reasons. Therapeutic areas of clinical trials in the control group were distributed as follows: oncology – 40 trials (39.2 %); infections – 20 trials (19.6 %); endocrine and metabolic diseases – 18 trials (17.6 %); nervous system – 6 trials (5.9 %); blood diseases – 6 trials (5.9 %); circulatory system – 4 trials (3.9 %);

respiratory system – 4 trials (3.9 %); and digestive system – 4 trials (3.9 %). 66 clinical trials (64.7 %) were phase III trials, 28 (27.5 %) were phase II trials, and 8 (7.8 %) were phase IV trials.

1.2.4. Primary endpoints

We analyzed whether overall survival (OS) was used as one of the primary endpoints in clinical trials. Outcome measures other than OS were classified as non-OS. Examples of such endpoints included disease-specific mortality, morbidity, clinical events, hospitalization, patient reported outcomes (symptoms, functioning, health-related QoL), physical signs, laboratory measures, biomarkers, radiological tests, response rates, progression-free survival (PFS), disease-free survival (DFS), pharmacokinetic (PK) parameters, and adverse events (AE). Only the primary endpoints were evaluated; secondary endpoints were not taken into account.

1.2.5. Comparators

Controls (comparators) were classified into the following types: placebo, different (active) treatment, different dose or regimen of the study drug (dose comparison), no treatment, or external (historical) control (EMA, 2001).

1.2.6. Data analysis

We used Fisher's exact test for statistical analysis of categorical variables: primary endpoints, randomization, masking, and comparators. T-test was used for scalar values: estimated trial duration and enrollment. 5 % was used as a significance level of the tests, considering that with $p<0.05$ the null hypothesis could be rejected.

1.3. Analysis of orphan medicinal products

1.3.1. Definition and identification of orphan drugs

Orphan drugs were defined as the medicinal products with European marketing authorization and European orphan designation granted by the EMA and active during the studied period. European Community Register of designated orphan medicinal products and the EMA database of rare disease designations were used to identify orphan drugs authorized in the EU.

1.3.2. Determination of orphan drug availability on Latvian market

Availability of orphan drugs on Latvian market was determined by using the National Register of Human Medicines maintained by the State Agency of Medicines of Latvia, as well as EUCERD 2012, 2013, and 2014 Reports, and directly contacting drug manufacturers and wholesalers. Drugs were considered to be available if they were marketed/ launched in Latvia according to data in at least two of the above mentioned sources.

1.3.3. Evaluation of orphan drug accessibility (reimbursement mechanisms) in Latvia

The National Health Service data were used to assess drug reimbursement including the national reimbursement list (as of January 2014) and individual reimbursement data in 2008–2012. Children's Clinical University Hospital purchase procedure reports on "Medicinal treatment for children with rare diseases" program in 2010–2014 were analyzed to identify orphan drugs

provided within this program. Drugs were considered to be accessible if they were provided within some of the reimbursement mechanisms mentioned above.

1.3.4. Definition and identification of surgery related orphan drugs

Summary of Product Characteristics (SPC) for all orphan drugs approved by the EMA were analyzed to find drugs with approved labeled indications related to surgery (used pre-, during or post-surgery). These indications were not necessarily orphan designated indications of orphan drugs with multiple labeled indications.

1.4. Impact of orphan drugs on Latvian budget – calculations and analysis

Our study covered a 5-year period, from 2010 to 2014. Some drugs, that were originally designated orphan medicines, are no longer considered orphan drugs in Europe. These products were withdrawn from the European Community Register of designated orphan medicinal products, either at the end of the period of market exclusivity or on the request of the sponsor. Such drugs were included in the study until the end of the year when the last orphan indication of the product was withdrawn, i.e. the last year these drugs were formally considered orphan medicines in Europe. For instance, Sutent was withdrawn from the European Community Register in 2008, and was, therefore, out of the scope of the current study, which covered the period of 2010–2014.

Impact of orphan drugs on Latvian budget was calculated from the National Health Service's (NHS) perspective. A particular orphan drug can have multiple indications, orphan and non-orphan. For such drugs, only expenditures related to orphan indications were taken into account. For assessment of orphan drug reimbursement, including the reimbursement lists and the individual

reimbursement, we used the NHS annual reports on the use of funds for reimbursement of outpatient drugs and medical devices. Children's Clinical University Hospital (CCUH) purchase procedure reports on the "Medicinal treatment for children with rare diseases" program (financed by the NHS) were analyzed to assess orphan drugs provided through this pathway. A particular orphan medicinal product can be provided through multiple reimbursement mechanisms. For such products, double counting was excluded.

Total drug reimbursement budget (orphan and non-orphan products) was calculated as a sum of funds covering the reimbursement lists, individual reimbursement and the CCUH program. This information was available from the NHS annual public reports. For the information on total pharmaceutical market (total turnover of medicines) we used "Statistics on Medicines Consumption" annually published by the State Agency of Medicines of Latvia. Budget impact of orphan drugs was calculated by dividing the expenditures covering orphan drugs by the total pharmaceutical market and the total drug reimbursement budget, respectively.

Euro (*EUR*) was introduced in Latvia on 1st January 2014, thus no currency conversion was required for this year. For the period 2010–2013, we used the official exchange rate defined by the Bank of Latvia for the national currency (Latvian lat – *LVL*). Starting from 2005, the Bank of Latvia set a fixed exchange rate 1 *EUR* = 0.7028 *LVL*, which was actual until the end of 2013. When the literature review was performed, for comparison with other countries, we used xe.com *EUR* exchange rates, if orphan drug expenditures were expressed in other currencies, e.g. British pounds (*GBP*).

Annual expenditure per patient was calculated by dividing the annual expenditure covering orphan drug reimbursement by the number of patients receiving these medications. For the individual reimbursement and the CCUH program, the number of patients receiving particular drugs was known from the

NHS annual reports on the use of funds for reimbursement of outpatient drugs and medical devices and the NHS annual public reports, respectively. For drugs included in one of the reimbursement lists, the number of patients was estimated by using the EMA approved summary of product characteristics (SPC) and the number of drug packages reimbursed by the NHS. The SPC was used to identify the recommended maintenance daily dose used for drug's main indication in adults. This dose was further converted to the number of pharmaceutical forms (e.g. tablets or capsules). Then, the content of a single package was divided by the number of pharmaceutical forms required per day, to find the duration of treatment (number of days) covered by one package. It was further calculated how many packages are required for one year treatment period. Number of patients receiving a particular drug was estimated by dividing the total number of drug packages reimbursed by the NHS by the number of packages required for one patient per year.

1.5. Comparison strategy with other European countries

A literature review was performed to compare the situation in the field of orphan drugs and the budget impact of these drugs in Latvia and other European countries. The budget impact of orphan drugs was expressed in absolute figures (million *EUR*) and relative to the total pharmaceutical market. If a study reported only the budget impact of orphan drugs as a percentage of the total pharmaceutical market, the absolute figures were calculated taking into account the numbers representing the total pharmaceutical market, as reported in the study. If multiple studies were available for a country, the most recent study was selected. If a study reported actual (observed) data and data forecasted for the future, the observed data for the latest year were preferred. The World Bank's data on the population and GDP (PPP) per capita were used for each country for the year of interest. We also identified the number of orphan drugs with active

marketing authorizations in the EU and converted the orphan drug expenditure into expenditure per 100 000 inhabitants.

2. RESULTS

2.1. Situation in the field of rare diseases in Latvia

2.1.1. National plan for rare diseases

Latvian national plan for rare diseases was written by the working group, which included health care professionals, representatives from the Ministry of Health (MoH) and patient organizations. The plan was submitted to the MoH for evaluation in December 2011 (Aymé and Rodwell, 2013; Logviss, Krievins and Purvina, 2014), and a public consultation of the plan was launched in 2012 and the results were subsequently analyzed by the MoH. A number of meetings with different stakeholders were held, and as a result, the MoH developed and on 20 June 2013 approved the National Plan for Rare Diseases for the period from 2013 to 2015 (Veselības ministrijas rīkojums Nr. 110, 2013) in accordance with the European Council recommendations of 8 June 2009 on an action in the field of rare diseases (Council Recommendation, 2009).

There is no official definition for rare diseases in Latvia, as stakeholders accept definition of the European Regulation on Orphan Medicinal Products of a prevalence of no more than 5 in 10 000 individuals, and that rare diseases are life-threatening or chronically debilitating (Aymé and Rodwell, 2013; Veselības ministrijas rīkojums Nr. 110, 2013). Main strategic objectives of the plan are related to improving access to information on rare diseases for health care professionals and patients with their families, as well as creation of rare disease patient register. An important role of the plan is dedicated to the prevention and early detection of rare diseases, integrated medical and social care for patients, and continuing education of health care professionals in the field of rare diseases.

On 23 October 2017, the second plan for rare diseases was approved for the period 2017–2020. The plan includes priority tasks and measures to be taken

to improve the early diagnostics, timely treatment and flow of information for rare diseases (Ministru kabineta rīkojums Nr. 602, 2017). The new plan is intended to ensure the availability of medicines and genetic tests not only for children, but also for adult patients with appropriate indications. A total of *EUR* 66.9 million is needed to carry out the activities mentioned in the plan, of which *EUR* 5 million in 2018, *EUR* 31.4 million in 2019, and *EUR* 30.5 million in 2020. Further, additional funding of *EUR* 30.5 million will be required annually.

2.1.2. Centers of expertise

There are currently no official designated centers of expertise for rare diseases in Latvia, but a meeting was held in 2013 to discuss possible criteria for national centers of expertise (Rodwell and Aymé, 2014). A legal framework for centers of expertise, including those for rare diseases, is expected in the future. Several medical centers, that fulfill this role, are currently recognized by reputation only (Aymé and Rodwell, 2013). For example, the CCUH provides genetic services, as well as services for children with haematological, oncological and endocrinological diseases. Riga East Clinical University Hospital (RECUH) has a specialized clinic of chemotherapy and haematology, in which patients with haemophilia A and B, factor XII deficiency and von Willebrand disease receive diagnostics and treatment. Rare oncological diseases, e.g. Burkitt's lymphoma, Langerhans cell histiocytosis, Mantle-cell non-Hodgkin's lymphoma, multiple endocrine neoplasia, Ewing's sarcoma, Wilms' tumour, Waldenstrom's macroglobulinaemia and others can be treated in this hospital as well. Pauls Stradins Clinical University Hospital (PSCUH) provides services in different rare disease areas, such as cardiology, angiology, pulmonology, nephrology, endocrinology, gastroenterology, oncology and ophthalmology. Latvian Pulmonary Hypertension Center is a part of Center of Cardiology of Latvian University located in PSCUH. The MoH, Orphanet

Latvian team and experts from the three university hospitals mentioned above met in 2013 and started work on developing criteria for national centers of expertise (Rodwell and Aymé, 2014). The Center of excellence for treatment and research of multidrug-resistant tuberculosis set up in the Latvian Infectology center in 2000 can be mentioned as an example for the development of potential regional reference centers in Latvia.

2.1.3. Patient registers

Currently there is no specific register for rare disease patients in Latvia making it impossible to fully collect and evaluate information on rare diseases, although the national plan for rare diseases foresees activities for evaluation and improvement of existing patient registers to start centralized data collection on rare disease patients (Rodwell and Aymé, 2014; Veselības ministrijas rīkojums Nr. 110, 2013). Register of Patients Suffering from Certain Diseases maintained by the Center for Disease Prevention and Control (CDPC) contains records on some rare diseases including cancers and congenital anomalies. Congenital Anomaly Register is a part of Register of Patients Suffering from Certain Diseases and it contained data on 11 990 patients with congenital anomalies as of June 2012 (Valsts informācijas sistēmu reģistrs, 2012). According to data from the Newborn Register 582 cases of congenital malformations were diagnosed in maternity wards in 2011 and 677 cases in 2012 (SPKC, 2012a). They calculated in 6.1 % of total newborns morbidity rate in 2012. However, data in the Congenital Anomaly Register is incomplete, since the register is not functioning optimally, because there is no mechanism in place that would regulate flow of information on newly diagnosed congenital anomalies (Veselības ministrijas rīkojums Nr. 110, 2013). Therefore the register in its current form requires big improvements as it is stated in the national plan for rare diseases. Genome Database of Latvian Population has been created and is maintained by Latvian

Biomedical Research and Study Center (BMC) (BMC, 2014). This database is a nationwide project designed to create identification, storage and processing system for health and genetic information of Latvian population for research, preventive and therapeutic purposes. As of November 2012 the number of participants recruited in the project (number of collected DNA samples) was 20 126 (P3G, 2013). DNA and data collection of monogenic diseases maintained by Genome Database of Latvian Population contains more than 800 patient samples (more than 500 of which for rare diseases) (Veselības ministrijas rīkojums Nr. 110, 2013).

Rare cancers are included in the National Cancer Control Program (2009–2015) adopted by the Cabinet of Ministers in 2009 (Ministru kabineta rīkojums Nr. 48, 2009). According to data of Latvian Cancer Register there were 71 166 patients registered at the end of 2012 (SPKC, 2013) (cancer was newly diagnosed in 11 534 patients in 2012). Taking into account that rare cancers calculate in 24 % of the total cancer prevalence in the EU (Gatta et al., 2011) (annual incidence rate of rare cancers in Europe is 22 % of all cancer diagnoses), the estimated number of patients with rare cancers in Latvia could be around 17 080 patients (annually around 2 537 newly diagnosed patients).

The Cardiovascular Health Improvement Action Plan (2013–2015) was adopted in 2013 (Ministru kabineta rīkojums Nr. 359, 2013). It includes activities in the fields of health promotion, improving cardiovascular disease treatment and early diagnostics of congenital malformation of the heart. According to data from the heart disease register of the CCUH clinic of children's cardiology and cardiac surgery 152 newborns (0.77 %) were diagnosed with congenital heart disease in 2012, 11.1 % of heart pathologies were diagnosed late and 55.5 % of pathologies were diagnosed antenatally.

Health care professionals from several university hospital centers collect rare disease patient data, for example, since 2007 there is a pulmonary arterial

hypertension (PAH) patient register at the Latvian Cardiology Center of PSCUH (Aymé and Rodwell, 2013). Center of Endocrinology of PSCUH has created several data bases of patients with rare endocrine diseases, such as acromegaly, Cushing's disease, and MEN (multiple endocrine neoplasia) syndrome (Rodwell and Aymé, 2014). These data bases were created for follow-up purposes, as well as to serve as a source of scientific information. Congenital anomaly register is held by the medical genetics clinic at the CCUH. According to CCUH data there are records on 40 cystic fibrosis patients in Latvia as of the end of 2013 (BKUS, 2014), and every year this diagnosis is confirmed in one child, on average. Data are also collected by rare disease patient organizations. For instance, according to Latvian Haemophilia Society data there are around 250 patients with bleeding disorders (Veselības ministrijas rīkojums Nr. 110, 2013), while Pulmonary Hypertension Association has data on 51 patients with diagnosed PAH.

It should be noted that implementation of the e-health project is planned to be launched in Latvia in 2014. Within this project data on patient health and received health care services will be stored centrally. There is also a pilot plan to use Orpha codes and OMIM codes for rare diseases within the e-health system to ensure identification and visibility of rare diseases (Rodwell and Aymé, 2014). Some activities are currently being implemented including the approval of an act concerning the plan to include Orpha codes in the congenital anomaly and cancer registers. It would allow using e-health system information for obtaining data on prevalence, diagnostics, and treatment of rare diseases. If the above mentioned plan was implemented, making new separate rare disease patient register would not necessarily be required (Veselības ministrijas rīkojums Nr. 110, 2013).

Despite the fact that the Congenital Anomaly Register contains records also for rare diseases (as of 14.06.2017, 324 rare diseases with Orpha codes for 1108 patients were registered there), the problem of rare disease patient registration still remains relevant (Ministru kabineta rīkojums Nr. 602, 2017),

which makes the long-term budget planning difficult. The amount of information contained in the existing patient registers does not reflect the actual number of patients with rare diseases, since data is not systematically entered there. In response to this issue, on 28 February 2018, the Rare Disease Coordination Center was set up in CCUH, with support units in PSCUH and RECUH, to provide services for both children and adult patients.

Latvia contributed to EUROCARE-5 (European Cancer Register Based Study on Survival and Care of Cancer Patients), RARECARENet (Information Network on Rare Cancers), EUROCAT (European Surveillance of Congenital Anomalies), and EUHASS (European Haemophilia Safety Surveillance) (Aymé and Rodwell, 2013). Latvian teams also participated in the following pilot European reference networks for rare diseases: Dyscerne (European Network of Centers of Expertise for Dysmorphology) and PAAIR (Patient Associations and Alpha-1 International Register) (Aymé and Rodwell, 2012). These pilot projects were financed by the European Commission within the scope of the Community action program on rare diseases, including genetic diseases (1999–2007) and the second program of the Community action in the field of health (2008–2013). Only one register of rare disease patients (Latvian cystic fibrosis patient register) is listed in Orphanet report on rare disease registers in Europe (Orphanet, 2014), which means that there is a need to improve information exchange and optimize flow of information among different institutions.

2.1.4. Diagnostics

Newborns are screened for only two rare disorders in Latvia: phenylketonuria (since 1987) and congenital hypothyroidism (since 1996) (Veselības ministrijas rīkojums Nr. 110, 2013). Data on newborns screened in maternity units are collected in the newborns register that is supervised by the CDPC (Rodwell and Aymé, 2014). An average of 22 neonates with congenital

hypothyroidism and 4 with phenylketonuria were annually diagnosed through this neonatal screening program in 2007–2012 (SPKC, 2012b). A question has been recently raised concerning expanding the newborn screening by using tandem mass spectrometry method (Veselības ministrijas rīkojums Nr. 110, 2013). Latvian Food and Veterinary Service and Institute of Organic Synthesis have such mass spectrometry devices, but they are not used for medical purposes making it a nonsense situation.

Some prenatal and postnatal diagnostic tests for rare genetic diseases are financed by the NHS (Veselības ministrijas rīkojums Nr. 110, 2013), including:

1) Cytogenetic analysis: chromosome analysis with the standard method and molecular cytogenetic or FISH (fluorescence in situ hybridization) method;
2) Genetic biochemical analysis: biochemical screening of pregnant women at high risk for fetal genetic abnormalities; neonatal screening for phenylketonuria and congenital hypothyroidism; selective screening of inborn metabolic disorders (spectrum of amino acids and organic acids, as well as analysis of oligosaccharides, mucopolysaccharides and carbohydrates);
3) DNA diagnostics for: spinal muscular atrophy, hereditary motor and sensory polyneuropathy, long chain and medium chain fatty acid oxidation disorders, Huntington's chorea, fragile X syndrome.

Additionally, diagnostics of the following genetic disorders are available within the scientific research projects or in laboratories of scientific institutions (Veselības ministrijas rīkojums Nr. 110, 2013): cystic fibrosis, hereditary haemochromatosis, Wilson's disease, Gilbert's syndrome, alpha-1 antitrypsin deficiency, several forms of inherited cancers, and thrombophilia. In some cases clinical university hospitals collaborate and send samples to BMC for genetic testing (Rodwell and Aymé, 2014). For example, genetic testing of all family

members of patients with MEN syndrome is financed in terms of scientific project. Genetic testing is available through Medical Genetics Clinic of CCUH, Molecular Genetics Scientific Laboratory of Riga Stradins University (RSU), and BMC (Aymé and Rodwell, 2013). In recent years amount of newly diagnosed genetic diseases has increased by about 25 % (Veselības ministrijas rīkojums Nr. 110, 2013) thanks to new diagnostic methods offered by these institutions. However, despite the progress made in the diagnostics of genetic diseases, number of patients with unspecified genetic abnormalities requiring additional investigation abroad is increasing. Genetic testing in other EU states is possible through the special E112/S2 forms, if genetic testing is a health care service usually financed from the state budget, but this service cannot be provided in Latvia or cannot be provided within a reasonable period of time (Aymé and Rodwell, 2013). Mostly it is provided for children with lifethreatening or treatable conditions.

Clinical guidelines for rare diseases have not been approved at the national level, although center of endocrinology of PSCUH in collaboration with endocrinologists from RECUH and CCUH issued diagnostic algorithms for rare endocrine diseases in 2013 (Rodwell and Aymé, 2014). These recommendations aim to help general practitioners and endocrinologists to consider rare endocrine diseases in certain types of patients. PSCUH also organizes post-diploma educational courses in most areas of medicine, including endocrinology. These courses usually cover not only common clinical conditions but rare diseases as well. As it is with some rehabilitation services described below, even in such small country as Latvia there are some regional differences in availability of diagnostics for rare diseases (Veselības ministrijas rīkojums Nr. 110, 2013), because Latvian health care system is organized in such a way that individual tests requiring modern technologies and complex manipulations are performed only by the university hospitals, which are concentrated in Riga. Further medical

care with less complex health services is provided by regional multi-profile hospitals.

2.1.5. Rehabilitation services

In parallel with timely and accurate diagnostics and appropriate treatment, rare disease patients require also proper rehabilitation services. State funding of medical rehabilitation and amount of provided services, including funding for assistive technologies (technical aids), has decreased significantly over the past few years (Veselības ministrijas rīkojums Nr. 110, 2013). Therefore current availability of rehabilitation services for rare disease patients is not sufficient. For instance, suitable solutions are still not found for such assistive technologies as special mobility devices for muscular dystrophy patients and oxygen devices for pulmonary hypertension patients. This problem is particularly actual outside Riga, where rehabilitation services are limited. Palliative care services for children are provided by a multidisciplinary palliative care team set up in CCUH. This team provides inpatient and outpatient consultative services to families as well as palliative care services at home for children in Riga. Palliative care services for children in other Latvian regions and cities (except Liepaja) are limited, despite the fact that the government supports development of these services. The reason of such differences could be partially explained by the fact, that there are certain requirements for the health care specialists to provide these services, as well difficulties are experienced in involvement of multidisciplinary team.

A new service for persons with disabilities (including disabilities due to rare diseases) was launched in January 2013 (Rodwell and Aymé, 2014). It is a municipality based service providing an assistant for performing activities outside home, e.g. to get to work, school or rehabilitation institution. The assistant service is eligible for persons from 18 years of age with group 1 or group

2 disability (very severe or severe disability, respectively), or persons aged 5–18 years without dividing disabilities into the groups. The assistant service is provided on the basis of conclusion of the State medical commission for the assessment of health condition and working ability.

2.1.6. Patient organizations

Latvian rare disease patient organization "Caladrius" was launched in 2009 (Aymé and Rodwell, 2012, 2013). Mission of this organization is to provide patients with relevant information in the field of rare diseases, as well as to support patients and represent their interests. "Caladrius" established a fund to help rare disease patients who could not otherwise pay for their treatment, and in collaboration with CCUH organized two visits of highly qualified cardiac surgeons in 2011. As a result complicated operations were carried out for eleven children with inborn heart pathologies.

There is a number of other rare disease related patient organizations in Latvia, including Haemophilia Society, Pulmonary Hypertension Association, Cystic Fibrosis Society, and Association of People with Special Needs "Motus Vita" (Rodwell and Aymé, 2014). These organizations often collaborate with each other, organize rare disease events and celebrate annual rare disease day. For example, Pulmonary Hypertension Association financially supported the first pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension (CTEPH) patient in 2013, organized the summer health camp, and proceeded the oxygen home care therapy supporting for PAH patients. Latvian Haemophilia Society intensified cooperation with Lithuanian Haemophilia Society in 2013 in order to provide disease specific training for physiotherapists working with people with bleeding disorders in CCUH and RECUH. Latvian Alliance for Rare Diseases, which brings together the five abovementioned rare disease patient organizations, was launched in 2014. The Alliance is also an

associate member of the European Organisation for Rare Diseases (EURORDIS).

2.1.7. Sources of information on rare diseases

MoH has designated the CDPC as a representative of Latvia to participate in Orphanet Europe Joint Action project (Aymé and Rodwell, 2013). Orphanet team is currently hosted by the CDPC and is in charge of collecting data on rare disease related services in Latvia, such as specialized clinics, medical laboratories, ongoing research, registers, clinical trials and patient organizations. Orphanet national website was launched in April 2012 and is regularly updated by the Orphanet team. Web based information is also available for a limited number of conditions through other sources of information on rare diseases, such as paediatric rheumatic diseases, lysosomal storage diseases, and through websites of patient organizations for pulmonary hypertension, cystic fibrosis, neuromuscular diseases, bleeding disorders, leukaemia and some other forms of cancer.

2.1.8. Scientific research projects

Generally funding is available for rare disease projects (through state budget, charities and pharmaceutical companies) (Aymé and Rodwell, 2013) although these funds are not specifically designed for rare disease research. Rare diseases were not included in the priority directions of science and research (Rodwell and Aymé, 2014), but a number of scientific research projects in the field of rare diseases take place in Latvia (Veselības ministrijas rīkojums Nr. 110, 2013). As well collaboration networks have been created with researchers from Baltic States and other countries around the world. Examples of such projects are researches in:

1) Hereditary liver, lung and mitochondrial diseases (Scientific Laboratory of Molecular Genetics, RSU);
2) Genetics of inherited cancers (Institute of Oncology, RSU);
3) Nonsyndromic hearing loss (Clinic of Medical Genetics, CCUH);
4) Nonsyndromic orofacial clefts, familial melanoma, MODY (maturity onset diabetes of the young) type diabetes, congenital muscular dystrophies and familial hypercholesterolaemia (BMC);
5) Genetics and effectiveness of treatment of acromegaly (PSCUH and BMC);
6) Genome analysis of rare hereditary eye disorders and metabolic abnormalities (collaborative project with the University of Tartu);
7) Rare cardiovascular diseases. Project coordinated by Center for Rare Cardiovascular Diseases, John Paul II Hospital in Krakow, Poland. Principal partners are Latvian Center of Cardiology, PSCUH and Lithuanian University of Medical Sciences, Kaunas.

Baltic Metabolic Group annually brings together experts in the field of metabolic diseases (Veselības ministrijas rīkojums Nr. 110, 2013). Research projects on inherited metabolic diseases in the Baltic region are carried out within the framework of this group. Latvia is currently an observer of the E-Rare (ERA-Net for research programs on rare diseases) project (Rodwell and Aymé, 2014), however Latvian funding agencies do not contribute to the IRDiRC (International Rare Disease Research Consortium) project.

2.2. Clinical trials

2.2.1. Clinical trials in rare diseases

A total of 51 interventional clinical trials related to rare diseases, which were conducted in Latvia, were identified through the EU Clinical Trials Register

(Table 2.1). 28 trials (54.9 %) involved investigational medicinal products (IMP) with orphan designation in the studied indication. A total of 35 unique IMP were studied in 29 different rare conditions. Oncology was the biggest therapeutic area, with 20 clinical trials (39.2 %), followed by infections, with 10 trials (19.6 %), and endocrine and metabolic diseases, with 9 trials (17.6 %). Multidrug-resistant tuberculosis (MDR-TB) was the most studied condition, with 7 trials (13.7 %), followed by chronic lymphocytic leukemia (CLL), with 4 trials (7.8 %), and chronic myelogenous leukemia (Ph+ CML), acromegaly, and *Pseudomonas aeruginosa* infection in cystic fibrosis, with 3 trials (5.9 %) in each condition. 33 clinical trials (64.7 %) were phase III trials (including two phase II/III trials), 14 (27.5 %) were phase II trials, and 4 (7.8 %) were phase IV trials.

Table 2.1

Clinical trials in rare diseases (05.2004–05.2016)*

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Bedaquiline (*Sirturo*)	MDR-TB	Phase II, RCT, double blind	Placebo	SCC	58	15	15	150
Bedaquiline (*Sirturo*)	MDR-TB	Phase II, open label	–	SCC	40.5	13	23	225
Bedaquiline (*Sirturo*)	MDR-TB	Phase III, RCT, double blind	Placebo	SCC	66	7	13	600
Delamanid (*Deltyba*)	MDR-TB	Phase II, RCT, double blind	Placebo	SCC; PK; AE	10	13	26	201
Delamanid (*Deltyba*)	MDR-TB	Phase II, open label extension	–	AE	14	80	100	430
Delamanid (*Deltyba*)	MDR-TB	Phase II, open label	–	AE; PK	17	20	30	30
Delamanid (*Deltyba*)	MDR-TB	Phase III, RCT, double blind	Placebo	SCC	59	60	150	390
Dopastatin (*BIM-23A760*)	Acromegaly	Phase II, open label	–	GH levels	8	10	24	24
Dopastatin (*BIM-23A760*)	Acromegaly	Phase II, open label	–	GH and IGF-1 levels	14	5	60	80

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Dopastatin (*BIM-23A760*)	Carcinoid syndrome	Phase II, open label	–	Symptom relief (diarrhea and/ or flushes)	17	10	60	80
Tobramycin (*TOBI Podhaler*)	Pseudomonas aeruginosa infection in CF	Phase III, RCT, double blind	Placebo	FEV1	12	6	40	100
Tobramycin (*TOBI Podhaler*)	Pseudomonas aeruginosa infection in CF	Phase III, open label extension	–	AE	12	6	40	100
Tobramycin (*TOBI Podhaler*)	Pseudomonas aeruginosa infection in CF	Phase III, open label extension	–	AE	9	3	40	100
Meropenem (*Meronem*)	Severe acute necrotizing pancreatitis	Phase IV, RCT, double blind	Placebo	Development of pancreatic or peripancreatic infection	27	40	240	240

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Somapacitan (*NNC0195-0092*)	Growth hormone deficiency	Phase III, RCT, double blind/ open label	Placebo (double blind), Somatropin (open label)	Truncal fat percentage	38.6	3	66	280
Claudiximab (*IMAB362*)	Gastric/ esophageal cancer	Phase II, open label	–	Rate of remission	17	8	25	30
Claudiximab (*IMAB362*)	Gastric/ esophageal cancer	Phase II, RCT, open label	*EOX* (epirubicin, oxaliplatin, capecitabine)	PFS; AE	41	65	85	231
Lanreotide (*Somatuline*)	Acromegaly	Phase IV, open label	–	Injection intervals (6 or 8 weeks) based on IGF-1 levels	24	20	110	150

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Lanreotide (*Somatuline*)	Carcinoid syndrome	Phase IV, RCT, double blind	Placebo	Usage of s/c octreotide as rescue medication to control symptoms (diarrhea and/ or flushing)	36	4	60	100
Recombinant microbial lipase (*SLV339*)	Exocrine pancreatic insufficiency due to chronic pancreatitis	Phase II, RCT, double blind	Placebo	CFA; CNA; stool parameters; nutritional parameters; clinical symptomatology; AE	6	30	60	80
Temozolomide (*Temodal*)	Glioblastoma multiforme	Phase III, RCT, open label	Dose comparison (conventional vs. dose-intensive temozolomid)	OS; PFS	48	40	834	834

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Catumaxomab (*Removab*)	Malignant ascites	Phase II/III, RCT, open label	Paracentesis	Puncture-free survival	21	36	168	216
Ovarian cancer vaccine (*CVac*)	Epithelial ovarian cancer	Phase II, RCT, double blind/ open label	Placebo (double blind), SOC (open label)	OS	60	15	244	286
Somatropin (*Somatropin Biopartners*)	Growth hormone deficiency	Phase III, RCT, open label	Somatropin (daily *Genotropin*)	Height velocity; AE	29	5	134	144
Teplizumab (*MGA031*)	Recent-onset type 1 diabetes mellitus	Phase II/III, RCT, double blind	Placebo	Total daily insulin dose; HbA1c levels	36	25	385	530
Bosutinib (*Bosulif*)	Ph+ CML	Phase III, RCT, open label	Imatinib (*Glivec*)	Complete cytogenetic response rate	108	30	206	412
Bosutinib (*Bosulif*)	Ph+ CML	Phase III, open label extension	–	AE (with special focus on diarrhea); BCR-ABL mutations; OS	84	2	136	500

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Ciprofloxacin DPI (*BAYQ3939*)	Non-CF bronchiectasis	Phase III, RCT, double blind	Placebo	Frequency of pulmonary exacerbations	34	28	200	400
Ciprofloxacin DPI (*BAYQ3939*)	Non-CF bronchiectasis	Phase III, RCT, double blind	Placebo	Frequency of pulmonary exacerbations	28	28	172	400
Duvelisib (*IPI-145*)	CLL/SLL	Phase III, RCT, open label	Ofatumumab (*Arzerra*)	PFS	72	22	174	307
Duvelisib (*IPI-145*)	CLL/SLL	Phase III, open label extension	Ofatumumab (*Arzerra*)	Overall response rate	24	22	174	307
Pazopanib (*Votrient*)	Renal cell carcinoma	Phase III, RCT, double blind	Placebo	PFS	24	10	175	400
Pazopanib (*Votrient*)	Renal cell carcinoma	Phase III, open label extension	–	AE	24	3	98	145
Sildenafil (*Revatio*)	Pulmonary arterial hypertension	Phase IV, RCT, double blind	Dose comparison (1/5/20 mg tid)	6MWT	29	5	82	219
Paclitaxel, micellar (*Paclical*)	Ovarian/ peritoneal/ fallopian tube cancer	Phase III, RCT, open label	Paclitaxel, *Cremophor EL* (*Taxol*)	CA-125 levels; PFS; hypersensitivity reactions	48	25	350	650

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Eprodisate disodium (*Kiacta*)	AA amyloidosis	Phase III, RCT, double blind	Placebo	CrCl; SCr; progression to end-stage renal disease	40	10	119	280
Obinutuzumab (*Gazyvaro*)	CLL	Phase III, open label	–	AE	55	7	560	800
Eltrombopag (*Revolade*)	ITP	Phase II, RCT, double blind	Placebo	Platelet count	18	10	129	422
Dinaciclib (*SCH-727965*)	CLL	Phase III, RCT, open label	Ofatumumab (*Arzerra*)	PFS	38	8	225	466
Lapatinib (*Tyverb*)	Squamous cell carcinoma of the head and neck	Phase III, RCT, double blind	Placebo	DFS	27	4	422	680
Tivantinib (*ARQ 197*)	Non-small cell lung cancer	Phase II, open label extension	–	AE	24	1	4	10
Masitinib (*AB1010*)	Mastocytosis	Phase III, RCT, double blind	Placebo	Symptom relief (pruritus, flushes, depression, and asthenia)	42	15	170	200

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Octocog alfa (*BAY 81-8973*)	Hemophilia A	Phase III, open label	–	Annualized number of bleeds	51	2	50	75
Clazosentan (*AXV-034343*)	Aneurysmal subarachnoid hemorrhage	Phase III, RCT, double blind	Placebo	Cerebral vasospasm-related morbidity; all-cause mortality	21	15	620	1146
Brivaracetam (*Briviact*)	Focal epilepsy/ POS	Phase III, RCT, double blind	Placebo	POS (type I seizures) frequency	43	40	350	900
Brivaracetam (*Briviact*)	Focal epilepsy/ POS	Phase III, open label extension	–	AE	68	40	274	720
Nilotinib (*Tasigna*)	Ph+ CML	Phase III, open label	–	Rate of molecular response	48	8	743	806
Ibandronic acid (*Bondronat*)	Multiple myeloma	Phase III, RCT, open label	Zoledronic acid (*Zometa*)	Skeletal related events	36	25	424	424

Table 2.1 continued

INN (trade name/ code name)	Condition	Trial design	Comparator	Primary endpoint	Estim. duration (months)	Estimated enrollment (number of subjects)		
						LV	EEA	Whole CT
Turoctocog alfa (*NovoEight*)	Hemophilia A	Phase III, open label extension	–	Frequency of development of FVIII inhibitors	90	8	36	215
Fingolimod (*Gilenya*)	Pediatric multip le sclerosis	Phase III, RCT, double blind	IFN β-1a (*Avonex*)	Annualized relapse rate	111	4	82	190
Pegylated reco mbinant human hyaluronidase (*PEGPH20*)	Pancreatic ductal adenocarcinoma	Phase III, RCT, double blind	Placebo	PFS; OS	47	24	224	420

INN – international nonproprietary name; CT – clinical trial; EEA – European Economic Area; MDR-TB – multidrug-resistant tuberculosis; RCT – randomized controlled trial; SCC – sputum culture conversion; PK – pharmacokinetics; AE – adverse events; GH – growth hormone; IGF-1 – insulin-like growth factor-1; CF – cystic fibrosis; FEV1 – forced expiratory volume in one second; PFS – progression-free survival; s/c – subcutaneous; CFA – coefficient of fat absorption; CNA – coefficient of nitrogen absorption; OS – overall survival; SOC – standard of care; HbA1c – hemoglobin A1c (glycated hemoglobin); Ph+ CML – Philadelphia chromosome positive chronic myelogenous leukemia; DPI – dry powder for inhalation; CLL – chronic lymphocytic leukemia; SLL – small lymphocytic lymphoma; tid – three times a day; 6MWT – six-minute walk test; CA-125 – cancer antigen 125; CrCl – creatinine clearance; SCr – serum creatinine; ITP – immune (idiopathic) thrombocytopenic purpura; DFS – disease-free survival; POS – partial onset seizure; FVIII – coagulation factor 8; IFN β-1a – interferon beta-1a.

* The detailed clinical trial protocol-related data (including the unique EudraCT number, start and end dates for each trial) are available through the web links to the EU Clinical Trials Register (clinicaltrialsregister.eu) provided in Appendix 1.

2.2.2. Characteristics of clinical trials in rare vs. common diseases

We found no significant difference in the use of OS as a primary endpoint in clinical trials between rare and non-rare diseases (9.8 % vs. 13.7 %, respectively; p=0.608) (Figure 2.1). However, clinical trials in rare diseases were less likely to be randomized controlled trials (62.7 % vs. 83.3 %; p=0.008) (Figure 2.2). Rare and non-rare disease clinical trials varied in masking, with rare disease trials less likely to be double blind (45.1 % vs. 63.7 %; p=0.035) (Figure 2.3). Active comparators were less frequently used in rare disease trials (36.4 % vs. 58.8 % of controlled trials; at a significance level of 10 %, as Fisher's exact test p=0.052) (Figure 2.4). Clinical trials in rare diseases enrolled fewer participants than those in non-rare diseases: in Latvia (mean 18.3 vs. 40.2 subjects; 95 % confidence interval (CI) of the difference 9.8–33.9; p=0.014) (Figure 2.5), in the EEA (mean 181.0 vs. 626.9 subjects; 95 % CI 239.3–652.5; p<0.001) (Figure 2.6), and in the whole clinical trial (mean 335.8 vs. 1406.3 subjects; 95 % CI 548.0–1593.0; p<0.001) (Figure 2.7). Although, we found no significant difference in trial duration between the groups (mean 38.3 vs. 36.4 months; 95 % CI -10.9–7.1; p=0.652) (Figure 2.8). All studies included in the analysis were multicenter and multinational trials involving multiple EEA member states and/ or being conducted both within and outside the EEA.

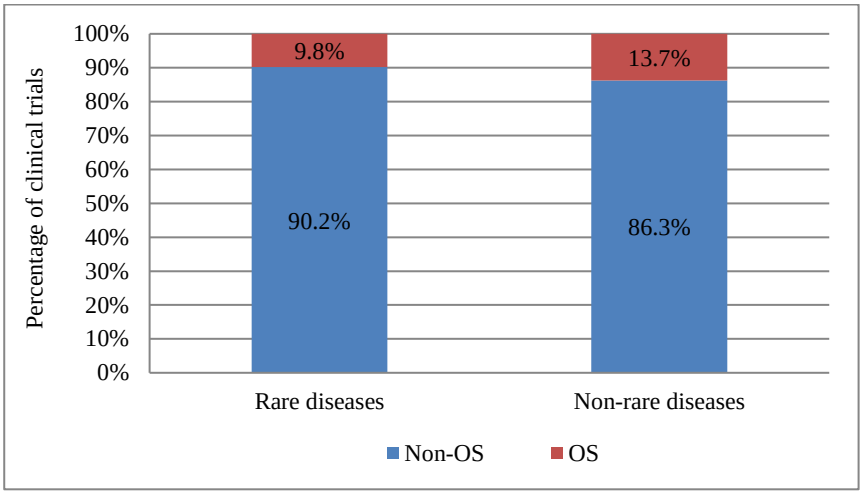

Figure 2.1. **Primary endpoints of clinical trials**

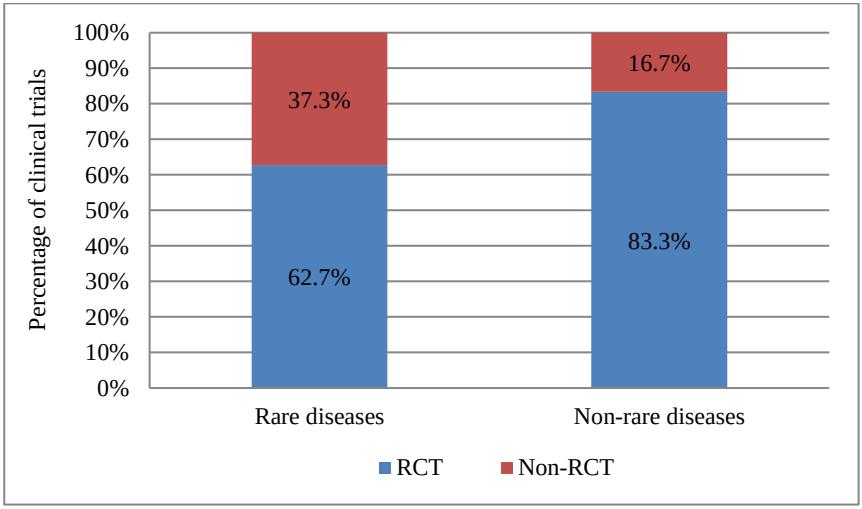

Figure 2.2. **Randomization of clinical trials**

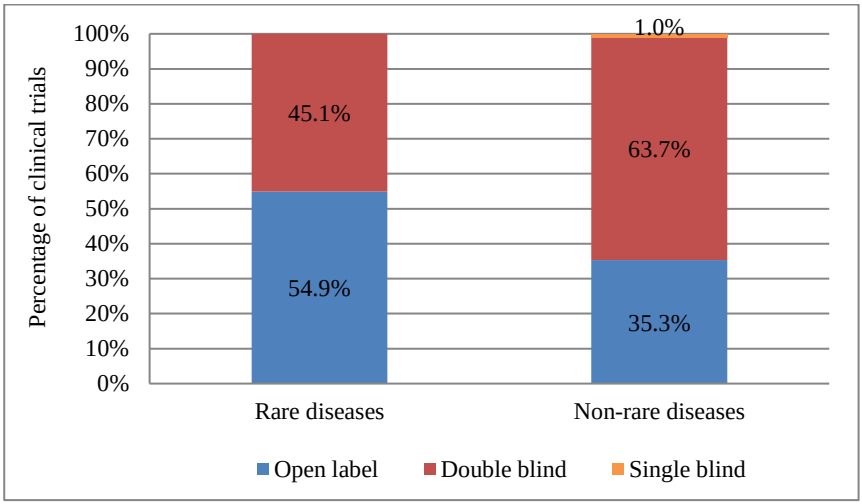

Figure 2.3. **Masking of clinical trials**

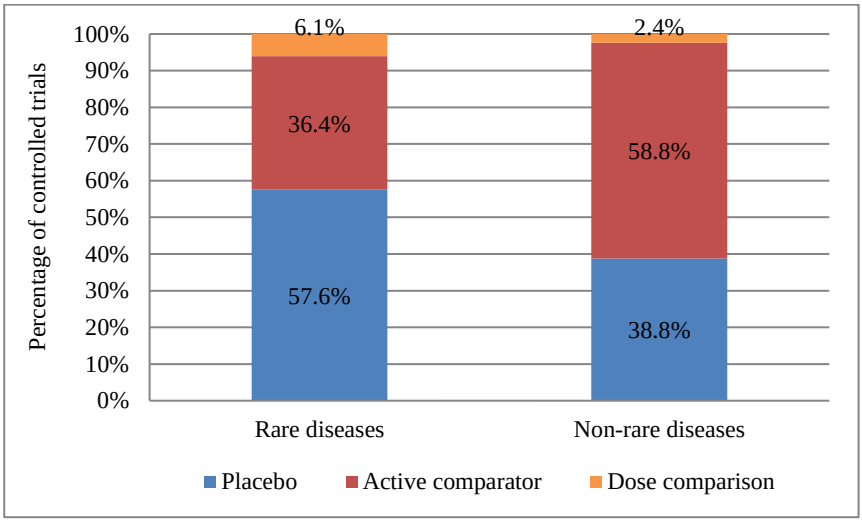

Figure 2.4. **Comparators of clinical trials**

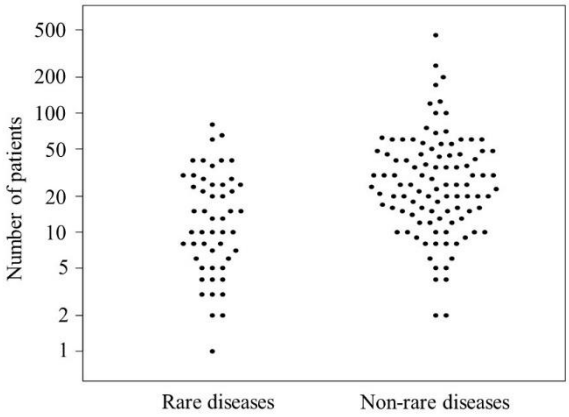

Figure 2.5. **Estimated trial enrollment in Latvia**

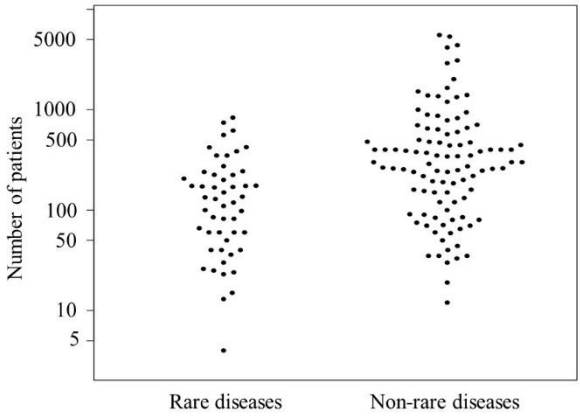

Figure 2.6. **Estimated trial enrollment in the EEA**

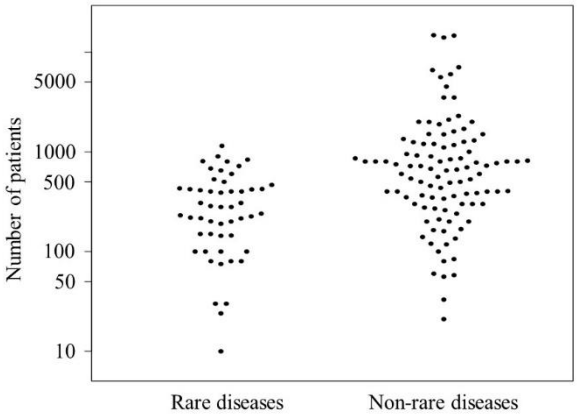

Figure 2.7. **Estimated enrollment in the whole clinical trial**

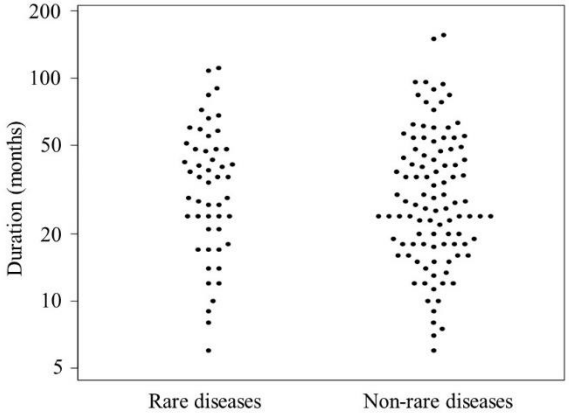

Figure 2.8. **Estimated trial duration**

2.3. Orphan medicinal products

2.3.1. Orphan drugs in Europe and Latvia

Pharmaceutical companies submit a single marketing authorization application to the EMA under the centralized procedure. Once granted by the European Commission, a centralized marketing authorization for orphan drug is valid in all the EU states (including Latvia). Whereas decisions surrounding orphan designation and marketing authorization of orphan medicines are taken at the EU level, decisions governing pricing and reimbursement of orphan drugs are a member state responsibility.

State Agency of Medicines (SAM) of Latvia includes medicinal products registered in Latvia as well as medicines centrally registered by the EMA in a register of medical products of the Republic of Latvia (Aymé and Rodwell, 2013). SAM is also responsible for regular collection and distribution of information on drugs, including orphan medicinal products, as well as for compiling information on drug safety, evaluating possible risks and coordinating measures for risk reduction. Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products reported that in Latvia SAM is entitled to make a decision regarding the fee exemption or reduction for activities associated with the evaluation or registration of a medicinal product if it (with or without orphan designation) is intended to the treatment of a rare disease (European Commission, 2005). The Inventory also stated that SAM may issue distribution authorization for medicinal product not registered in Latvia if it is intended for treatment of a rare disease (for an individual patient on the basis of prescription or for use in a health care institution on the basis of a written request).

A first level of accessibility exists for orphan medicines that have not yet been authorized, the most common being compassionate use. It covers diseases

for which no satisfactory alternative therapy exists. SAM has approved several programs for drug compassionate use in Latvian hospitals (Akuličs, 2012). The programs include influenza drugs (oseltamivir and zanamivir) for intravenous administration, medicine for chronic hepatitis C (boceprevir), and drugs for cancer (*Sprycel* and *Votrient*) used in Ph+ CML and metastatic soft tissue sarcoma, respectively. *Sprycel* is an orphan drug included in the national reimbursement list C, while *Votrient* was originally designated an orphan medicine, but it was further withdrawn from the EU register of designated orphan medicinal products upon request of the sponsor.

2.3.2. Orphan drug availability on Latvian market

As of April 2014, 34 orphan drugs were available on Latvian market (Table 2.2), including 6 drugs that are no longer considered to be orphan medicines in the EU. These drugs were originally designated orphan medicines, but further withdrawn from the EU register of designated orphan medicinal products either upon request of the sponsor (*Afinitor*, *Glivec*, *Revolade* and *Sutent*) or at the end of the period of market exclusivity (*Aldurazyme* and *Ventavis*). Strictly speaking it means that only 28 pure orphan products were available in Latvia, calculating in 38.9 % out of 72 orphan drugs authorized in the EU.

Table 2.2

Orphan drugs available in Latvia (04.2014)

Trade name	Active substance	Indication	Reimbursement
*Afinitor**	Everolimus	Neuroendocrine tumours of pancreatic origin (pNET) Renal cell carcinoma (RCC)	–
*Aldurazyme**	Laronidase	Mucopolysaccharidosis I (MPS I)	CCUH
Arzerra	Ofatumumab	CLL	Individual
Atriance	Nelarabine	T-cell ALL T-cell lymphoblastic lymphoma	Individual
Carbaglu	Carglumic acid	Hyperammonaemia	–
Cystadane	Betaine anhydrous	Homocystinuria	CCUH Individual
Diacomit	Stiripentol	Severe myoclonic epilepsy in infancy (Dravet's syndrome)	Individual
Elaprase	Idursulfase	MPS II (Hunter syndrome)	CCUH
Evoltra	Clofarabine	ALL	–
Exjade	Deferasirox	Beta thalassaemia major with iron overload due to blood transfusion	Individual
Gliolan	5-aminolevulinic acid	Malignant glioma	–
*Glivec**	Imatinib	Ph+ CML GIST Dermatofibrosarcoma protuberans Ph+ ALL Hypereosinophilic syndrome Myelodysplastic/ myeloproliferative diseases	List A (previously list C) Individual
Increlex	Mecasermin	Primary insulin-like growth factor 1 deficiency	CCUH

Table 2.2 continued

Trade name	Active substance	Indication	Reimbursement
Jakavi	Ruxolitinib	Myelofibrosis	–
Kuvan	Sapropterin	Hyperphenylalaninaemia in patients with phenylketonuria or tetrahydrobiopterin deficiency	CCUH
Litak	Cladribine	Hairy cell leukaemia	–
Mozobil	Plerixafor	Haematopoietic stem cell transplantation in lymphoma or multiple myeloma patients	Individual
Myozyme	Alglucosidase alpha	Pompe disease	–
Nexavar	Sorafenib	Hepatocellular carcinoma RCC	Individual
Nplate	Romiplostim	ITP	Individual
Orfadin	Nitisinone	Hereditary tyrosinaemia type 1	–
Pedea	Ibuprofen	Patent ductus arteriosus in preterm newborns	–
Peyona	Caffeine citrate	Primary apnea of premature newborns	–
Revatio	Sildenafil	PAH	Individual
*Revolade**	Eltrombopag	ITP	Individual
Sprycel	Dasatinib	Ph+ CML Ph+ ALL	List C (previously individual)
*Sutent**	Sunitinib	GIST RCC pNET	Individual
Tasigna	Nilotinib	Ph+ CML	List C
Tobi Podhaler	Tobramycin	Pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis patients	–

Table 2.2 continued

Trade name	Active substance	Indication	Reimbursement
*Ventavis**	Iloprost	PAH	–
Volibris	Ambrisentan	PAH	Individual
Votubia	Everolimus	Renal angiomyolipoma or subependymal giant cell astrocytoma associated with tuberous sclerosis complex	–
Wilzin	Zinc	Wilson's disease	Individual
Yondelis	Trabectedin	Soft tissue sarcoma Ovarian cancer	–

**Afinitor*, *Aldurazyme*, *Glivec*, *Revolade*, *Sutent* and *Ventavis* are no longer considered to be orphan medicines in the EU.

Orphan medicines are distributed by both hospital and community pharmacies. It should be noted that some of orphan drugs were stated as available in the SAM medicinal product register, however they were not considered to be available in Latvia, as they did not meet the availability criteria defined in the current study (i.e. drugs were considered to be available if they were marketed/launched in Latvia according to data in at least two of the sources mentioned in the Methods section). For example, *Torisel* was stated as available in the SAM register, although drug manufacturer has confirmed the opposite. Additionally, the individual reimbursement data showed that *Torisel* was reimbursed for two patients with malignant neoplasm of kidney in 2008. According to the company, *Somavert* (which is no longer an orphan medicine in Europe due to expiration of the period of market exclusivity) was available shortly after registration, but there was no demand, so the product is no longer available. As stated by the wholesalers, *Tracleer* and *Vidaza* were once in stock, but are not available anymore. The manufacturers also confirmed that these products are not available in Latvia.

There was no information on *Gliolan* availability provided in the SAM register, although the drug was stated as available in the EUCERD reports, and the product availability was also confirmed by the manufacturer and the wholesaler. There are special requirements for use of *Gliolan*. It should only be used by experienced neurosurgeons who have completed a training course in fluorescence-guided surgery (fluorescence microscope is used in the procedure) in malignant glioma resection. The marketing authorization holder (MAH) is obligated to implement the mentioned training course. According to information provided by the MAH, there was one neurosurgeon in Latvia experienced in utilizing the product. The SAM register provided no information on availability of *Diacomit*, however the product was stated as available in the EUCERD reports, as well it was individually reimbursed annually in 2008–2012. There was

also no information on *Aldurazyme* availability in the SAM register, although the company confirmed that the product was available. *Aldurazyme* was also stated as available in the EUCERD 2013 report. Additionally, it was purchased by CCUH within the "Medicinal treatment for children with rare diseases" program in 2014.

For some orphan drugs, the manufacturers stated that these products would be available on demand if there was a patient requiring them, as it was in case of *Atriance*, *Orfadin*, *Yondelis*, *Savene*, *Litak* and *Vpriv*. *Yondelis* has been provided by the company free of charge for one time, but it did not affect further availability of the drug. Several packages of *Ventavis* were bought quite rarely and were available only for patients in PSCUH. *Afinitor* was also available, and according to the company's information there could be around six patients in Latvia requiring treatment with this drug.

2.3.3. Orphan drug accessibility (reimbursement mechanisms) in Latvia

There is no specific policy in place for pricing of orphan drugs in Latvia. Costs related to rare diseases and orphan drugs are currently included in the national health care budget (Aymé and Rodwell, 2013; Veselības ministrijas rīkojums Nr. 110, 2013). Drug reimbursement covers drugs which are included in the national reimbursement drug list, or based on the medical council's decision, drugs can also be reimbursed within the framework of individual reimbursement system, with a limit of *EUR* 14 229 (previously *LVL* 10 000) per patient per year (Ministru kabineta noteikumi Nr. 899, 2006). The main principle of drug inclusion in the reimbursement list is that the drug should be therapeutically and cost effective, i.e. the decision is value based and is not specific to orphan drugs. The national reimbursement list consists of three parts:

list A covering therapeutically equivalent drugs (generics); list B that consists of drugs without therapeutic equivalent; and list C that contains drugs for which the annual cost exceeds *EUR* 4 269 (previously *LVL* 3 000) per patient and the manufacturer is obliged to cover treatment expenses for a certain number of patients with his own resources (not less than 10 %). The NHS evaluates therapeutic value, price, expected budget impact and cost-effectiveness for each drug before it is included in the reimbursement list. Drug price is compared with the prices in other EU countries. The price of the reimbursed medicine should not be higher than the third lowest price in the Czech Republic, Denmark, Romania, Slovakia and Hungary, and shall not exceed the price of the medicine in Estonia and Lithuania.

Health care of rare disease patients under 18 years of age is generally evaluated satisfactorily (Veselības ministrijas rīkojums Nr. 110, 2013). Since 2009, several orphan medicinal products for children are provided as a part of the state funded program "Medicinal treatment for children with rare diseases" coordinated by CCUH (Aymé and Rodwell, 2013; Veselības ministrijas rīkojums Nr. 110, 2013). Five orphan drugs (14.7 %) were provided within this program in 2010–2014: *Elaprase*, *Cystadane*, *Increlex*, *Kuvan* and *Aldurazyme*. However, after reaching the age of 18 and moving into adult patient group, most patients lose state support for reimbursement of medications and rehabilitation services. Another positive example of rare disease management in Latvia is a care of children with cystic fibrosis with a multidisciplinary team approach involving paediatricians, geneticists, pulmonologists, psychologists and social workers.

Orphan medicinal products are partially accessible via the reimbursement system. For a long time, *Glivec*, *Sprycel* and *Tasigna* were the only three drugs (8.8 %) included in the positive reimbursement list. *Glivec* was among the first orphan drugs available in Latvia (since 2001). It became the first and at that time the only orphan drug included in reimbursement list C and reimbursed for

Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) second line treatment. Starting from May 2013, *Glivec* was moved to the reimbursement list A, because cheaper generic drugs became available that changed prescribing and reimbursement criteria for imatinib. It can be prescribed by haematologist or paediatric haemato-oncologist based on the council's decision and is reimbursed for patients with Ph+ CML or acute lymphoblastic leukaemia (Ph+ ALL), bone marrow transplant, and gastrointestinal stromal tumours (GIST). *Sprycel* and *Tasigna* are reimbursed based on the haematologist council's decision for adult patients with Ph+ CML in chronic phase if prior therapy with imatinib was not effective (second line treatment).

Not more than two percent of the national drug reimbursement budget is intended to individual reimbursement, with limitation up to *EUR* 14 229 per patient per year. Fifteen orphan medicinal products (44.1 %) were provided within this individual reimbursement program in 2008–2012: *Arzerra*, *Atriance*, *Cystadane*, *Diacomit*, *Exjade*, *Glivec*, *Mozobil*, *Nexavar*, *Nplate*, *Revatio*, *Revolade*, *Sprycel*, *Sutent*, *Volibris* and *Wilzin*. Until January 2013, *Revolade* and *Arzerra* were reimbursed within the framework of individual reimbursement system. Starting with January 2013, regulation of the Cabinet of Ministers on individual drug reimbursement was changed. According to the new regulation, the individual reimbursement can be provided only in cases when diagnosis is not included in the reimbursement list or the diagnosis is included in the list, but there are no drugs included in the reimbursement list for treatment of this diagnosis. In case of *Arzerra* and *Revolade*, both diagnoses, chronic lymphocytic leukaemia (CLL) and immune (idiopathic) thrombocytopenic purpura (ITP), respectively, are included in the reimbursement list with some therapy alternatives available, making *Arzerra* and *Revolade* practically inaccessible for patients. Similar situation may refer to other orphan drugs previously provided within the individual reimbursement mechanism. For instance, only about a half

of *Volibris* price is covered by the state within the individual reimbursement system, while the rest is provided by the company or paid by patients. In case of *Nexavar* the state coverage is even smaller accounting in less than a quarter of price, therefore it is almost exclusively bought by individual patients for their own money (for some patients a quarter of price is paid by the NHS, but the rest is paid by the manufacturer). However, there are some positive exceptions, for example, reimbursement costs of *Revatio* do not exceed the limit of *EUR* 14 229 and it is therefore fully covered by the state. Besides, *Revatio* was reimbursed most frequently among all orphan drugs within the individual reimbursement system in 2008–2012.

A significant problem faced by rare disease patients is associated with special nutrition and medical foods. While some of these foods are vital for rare disease patients, they are usually not classified as medicinal products in Latvia. For some rare diseases, medical food often is the main or even the only way in which food is taken and its discontinuation can be life-threatening. So far, there is no standard procedure (regulation) in place for registration of medical food in Latvia (Veselības ministrijas rīkojums Nr. 110, 2013) and the manufacturer can choose the most appropriate registration procedure to him, most often based on cost considerations. As a result, it is not possible to adapt the same reimbursement arrangement for these foods as it is for medicinal products included in the national reimbursement drug list.

2.3.4. Orphan drugs in surgery

A total of 15 orphan drugs were identified that are used pre-, during or post-surgery (Table 2.3). 8 drugs (53.3 %) are used against different kinds of tumors, 4 of them (26.7 %) being used in stem or progenitor cell transplantation. As well dexrazoxane is used for treatment of anthracycline extravasation (an

antidote to anthracyclines, which are widely used anticancer medicines) making oncology even wider area for orphan drugs.

Table 2.3

Orphan drugs associated with surgery (03.2013)

Active substance	Trade name	Approved labeled indication
Concentrate of proteolytic enzymes enriched in bromelain	*NexoBrid*	Removal of eschar in patients with deep partial- and full-thickness thermal burns
Romiplostim	*Nplate*	Treatment of chronic idiopathic thrombocytopenic purpura (ITP) in splenectomised patients who are refractory to other treatments (corticosteroids, immunoglobulins)
Eltrombopag	*Revolade**	
Teduglutide	*Revestive*	Treatment of short bowel syndrome. Patients should be stable following a period of intestinal adaptation after surgery
Ibuprofen	*Pedea*	Treatment of a hemodynamically significant patent ductus arteriosus in preterm newborn infants
Ziconotide	*Prialt*	Treatment of severe, chronic pain in patients who require intrathecal analgesia
Dexrazoxane	*Savene*	Treatment of anthracycline extravasation
Celecoxib	*Onsenal***	Reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance
5-aminolevulinic acid	*Gliolan*	Visualization of malignant tissue during surgery for malignant glioma
Mifamurtide	*Mepact*	Treatment of high-grade resectable non-metastatic osteosarcoma in children, adolescents and young adults after macroscopically complete surgical resection
Imatinib	*Glivec**	Adjuvant treatment of patients who are at significant risk of relapse following resection of Kit (CD117)-positive gastrointestinal stromal tumors (GIST)
Brentuximab vedotin	*Adcetris*	Treatment of relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant

Table 2.3 continued

Active substance	Trade name	Approved labeled indication
Busulfan	*Busilvex*	Conditioning treatment prior to conventional hematopoietic progenitor cell transplantation (HSCT)
Thiotepa	*Tepadina*	Conditioning treatment prior to allogeneic or autologous HSCT in hematological diseases; when high dose chemotherapy with HSCT support is appropriate for the treatment of solid tumors
Plerixafor	*Mozobil*	Mobilisation of haematopoietic stem cells to the peripheral blood for subsequent autologous transplantation in patients with lymphoma and multiple myeloma

* *Glivec* and *Revolade* are no longer considered to be orphan medicines in the EU.
** *Onsenal* is now withdrawn from use in the EU.

Romiplostim and eltrombopag both are used for idiopathic thrombocytopenic purpura, although eltrombopag (as well as imatinib) was originally designated an orphan medicine, it was withdrawn from the EU register of designated orphan medicinal products upon request of the sponsor. A concentrate of proteolytic enzymes enriched in bromelain (*NexoBrid*) is used to reduce the need and extent of surgical removal of burnt tissue and/or skin transplantation. Wound area left with eschar may require further removal by surgery. According to the EMA requirements, distribution of *NexoBrid* should be controlled to ensure that the product is not available for use at a centre, until at least one surgeon at the centre has received formal training in the use of product.

Marketing Authorization Holder (MAH) for *Onsenal* has not been able to provide the additional data required to fulfill its specific obligation, as a result of slow enrolment in an ongoing clinical trial for familial adenomatous polyposis, therefore the product was voluntarily withdrawn from use in the EU in March 2011. However celecoxib is a non-steroidal anti-inflammatory drug (NSAID), marketed by the same manufacturer and in same pharmaceutical form (hard

capsules) under the trade name *Celebrex*, for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and thus it can potentially be used off-label. Another NSAID that is very widely available over the counter is ibuprofen, which is a designated orphan medicine named *Pedea* for patent ductus arteriosus treatment in preterm newborn infants. While ibuprofen is mainly used as tablet or oral suspension, *Pedea* is marketed as solution for injection. A course of therapy is defined as three intravenous injections given in 24 hour intervals. The first injection should be given after the first 6 hours of life. If the ductus arteriosus does not close 48 hours after the last injection or if it reopens, a second course of three doses may be given. If the condition is unchanged after the second course of therapy, surgery of the patent ductus arteriosus may then be necessary.

In case of ziconotide studies, the etiologies of pain were varied and included spinal pain, mostly due to failed back surgery. While the overall purpose of dexrazoxane trials was to investigate the efficacy of intravenously administered drug in preventing tissue damage from accidentally extravasated anthracycline, and thus preventing the patients from undergoing the routinely used surgical excision of the affected tissue. A blockbuster anticancer drug imatinib (*Glivec*) is presented in the current study, since one of its indications is adjuvant treatment of patients who are at significant risk of relapse following resection of Kit (CD117) positive gastrointestinal stromal tumors. Although originally it was designated an orphan medicine for wide range of oncological conditions: treatment of chronic myeloid leukemia, malignant gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, acute lymphoblastic leukemia, chronic eosinophilic leukemia (hypereosinophilic syndrome), and myelodysplastic/myeloproliferative diseases.

6 out of 15 orphan drugs (40 %) included in the analysis were available on Latvian market (Table 2.4). However availability of drugs does not mean that

they are really affordable, making drug reimbursement an important issue. Only one (6.7 %) orphan drug, imatinib, was included in the reimbursement list C (currently list A). Drugs included in the list are reimbursed for a particular indication, but not for all labeled indications. For imatinib, the reimbursed conditions were chronic myeloid leukemia and bone marrow transplantation. Other drugs could potentially be reimbursed within the framework of individual reimbursement system. Although in 2008–2012, only 3 drugs were reimbursed though this mechanism: romiplostim, eltrombopag, and plerixafor. There are special requirements for use of *Gliolan*. It should only be used by experienced neurosurgeons who have completed a training course in fluorescence guided surgery (fluorescence microscope is used in the procedure) in malignant glioma resection. MAH is obligated to implement the mentioned training course. According to information provided by the MAH, there was one neurosurgeon in Latvia experienced in utilizing the product.

Table 2.4

Surgery related orphan drugs available in Latvia (03.2013)

Active substance	Trade name	Reimbursement category	Reimbursement conditions
Imatinib	*Glivec**	List C (currently list A) Individual	Ph+ CML; bone marrow transplantation
Romiplostim	*Nplate*	Individual	Has been reimbursed for essential (hemorrhagic) thrombocythemia
Eltrombopag	*Revolade**		Has been reimbursed for neoplasms of uncertain or unknown behavior of lymphoid, hematopoietic and related tissue
Plerixafor	*Mozobil*		Has been reimbursed for nodular sclerosis and follicular lymphoma

Table 2.4 continued

Active substance	Trade name	Reimbursement category	Reimbursement conditions
5-aminolevulinic acid	*Gliolan*	–	These drugs were available in Latvia, but were neither included in the reimbursement list, nor reimbursed individually in 2008-2012
Ibuprofen	*Pedea*		

* *Glivec* and *Revolade* are no longer considered to be orphan medicines in the EU.

The NHS also maintains a list of drugs used in hospitals, which are needed for inpatient health care services funded by the state. No orphan drugs included in the analysis were found in the list. If a hospital requires a broader range or some specific products to provide services, an additional, hospital specific list of medicines should be maintained. In the current economic situation, covering drugs for rare diseases from the hospital budget is doubtful, taking into account high prices of orphan drugs. As an exception CCUH might be mentioned, as it manages a program of medicinal treatment of rare diseases in children and additional budget resources are available for this program.

2.4. Impact of orphan drugs on Latvian budget

Twenty one different orphan drugs were reimbursed through the three reimbursement pathways during the period covered by the study (Tables 2.5, 2.6, 2.7 and 2.8). The number of orphan medicines reimbursed per year increased slightly, from 11 drugs in 2010 to 15 drugs in 2014. Four drugs were provided through multiple reimbursement mechanisms: *Sprycel* and *Wilzin* were provided individually prior to inclusion in the reimbursement list; *Glivec* was simultaneously reimbursed individually and through the reimbursement list; *Cystadane* was provided through the individual reimbursement and the CCUH program. *Nplate* and *Mozobil* were included in the reimbursement list in 2014

and 2015, respectively, however so far these products were reimbursed individually. *Aldurazyme* and *Sutent* were reimbursed after the loss of orphan drug status in the EU, and were, therefore, excluded from the study.

Table 2.5

Orphan drugs included in the reimbursement lists (01.2010–12.2014)

Trade name	Active substance	Orphan indication	Inclusion date	Reimbursement list
*Glivec**	Imatinib	Ph+ CML; Ph+ ALL; MDS/MPD; GIST; DFSP; HES and CEL	April 2013	List A Previously List C
Nplate	Romiplostim	Idiopathic thrombocytopenic purpura (ITP)	March 2014	List B
*Wilzin**	Zinc	Wilson's disease	June 2014	
*Sutent**	Sunitinib	GIST	December 2014	
Sprycel	Dasatinib	Ph+ CML; Ph+ ALL	October 2010	List C
Tasigna	Nilotinib	Ph+ CML	December 2010	
Mozobil	Plerixafor	HSCT in patients with lymphoma and multiple myeloma	January 2015	

*Drugs withdrawn from the European Community register of designated orphan medicinal products

Table 2.6

Orphan drugs reimbursed within the CCUH program (01.2010–12.2014)

Trade name	Active substance	Orphan indication
Elaprase	Idursulfase	Mucopolysaccharidosis II (MPS II)
Myozyme	Alglucosidase alpha	Pompe disease
*Aldurazyme**	Laronidase	Mucopolysaccharidosis I (MPS I)
Kuvan	Sapropterin	Hyperphenylalaninaemia (HPA) in patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency
Cystadane	Betaine	Homocystinuria

Table 2.6 continued

Trade name	Active substance	Orphan indication
Increlex	Mecasermin	Primary insulin-like growth factor 1 deficiency
Votubia	Everolimus	Renal angiomyolipoma and subependymal giant cell astrocytoma associated with tuberous sclerosis complex (TSC)

*Drugs withdrawn from the European Community register of designated orphan medicinal products

Table 2.7

Individually reimbursed orphan drugs (01.2010–12.2014)

Trade name	Active substance	Orphan indication
Revatio	Sildenafil	Pulmonary arterial hypertension (PAH)
Volibris	Ambrisentan	PAH
*Tracleer**	Bosentan	PAH; systemic sclerosis
Nexavar	Sorafenib	Hepatocellular carcinoma; renal cell carcinoma; differentiated (papillary/follicular) thyroid carcinoma
Atriance	Nelarabine	T-ALL and T-LBL
*Sutent**	Sunitinib	GIST
*Glivec**	Imatinib	Ph+ CML; Ph+ ALL; MDS/MPD; GIST; DFSP; HES and CEL
Sprycel	Dasatinib	Ph+ CML; Ph+ ALL
Mozobil	Plerixafor	HSCT in patients with lymphoma and multiple myeloma
Arzerra	Ofatumumab	Chronic lymphocytic leukaemia (CLL)
Nplate	Romiplostim	ITP
*Revolade**	Eltrombopag	ITP
Exjade	Deferasirox	Chronic iron overload due to blood transfusions in patients with beta thalassaemia major, other anaemias, and non-transfusion-dependent thalassaemia syndromes
*Wilzin**	Zinc	Wilson's disease
Cystadane	Betaine	Homocystinuria
Diacomit	Stiripentol	Dravet's syndrome (Severe myoclonic epilepsy in infancy – SMEI)

*Drugs withdrawn from the European Community register of designated orphan medicinal products

Table 2.8

Drugs withdrawn from the European Community register of designated orphan medicinal products (12.2014)

Trade name	Active substance	Withdrawal date	Reason of withdrawal
Aldurazyme	Laronidase	June 2013	End of the period of market exclusivity
Wilzin	Zinc	October 2014	
Revolade	Eltrombopag	January 2012	Request of the sponsor
Sutent	Sunitinib	July 2008	
Glivec	Imatinib	November 2011	End of the period of market exclusivity (for Ph+ CML)
		April 2012	Request of the sponsor (for other indications)
Tracleer	Bosentan	May 2012	End of the period of market exclusivity (for PAH)
		April 2014	Request of the sponsor (for systemic sclerosis)

Orphan drug annual expenditure ranged between *EUR* 2.065 and 3.065 million, with total 5-year expenditure *EUR* 12.467 million (Tables 2.9 and 2.10). It constituted, on average, 0.84 % of the total pharmaceutical market annually, with a maximum 1.04 % seen in 2012, followed by a minimum 0.70 % in 2013. These peak and bottom values can be explained by the fact that *Glivec* was withdrawn from the European Community register of designated orphan medicinal products in 2012, and was no longer considered orphan medicine in the EU. Additionally, after the patent expiration in 2013, imatinib generics became available and practically replaced the brand drug from Latvian drug reimbursement system. Orphan drugs represented, on average, 2.14 % of the total drug reimbursement annual budget, with maximal (2.62 %) and minimal (1.83 %) values also observed in 2012 and 2013.

Table 2.9

Budget impact of individual orphan drugs (01.2010–12.2014)

Trade name	Active substance	Expenditure (EUR)						Share of total expend.	Reimb. category
		2010	2011	2012	2013	2014	Total		
Atriance	Nelarabine	24 773	–	–	–	–	24 773	0.20 %	Individual Reimbursement
Nexavar	Sorafenib	16 418	12 040	23 806	17 786	14 229	84 278	0.68 %	
Revatio	Sildenafil	104 742	147 370	219 252	340 536	480 685	1 292 585	10.37 %	
Volibris	Ambrisentan	52 172	87 744	142 289	128 058	163 633	573 897	4.60 %	
Exjade	Deferasirox	5 726	–	–	–	7 329	13 055	0.10 %	
Sprycel	Dasatinib	60 450	–	–	–	–	60 450	0.48 %	
Wilzin	Zinc	1 317	169	–	–	–	1 486	0.01 %	
Cystadane	Betaine	1 038	3 142	2 094	4 327	6 560	17 161	0.14 %	
Diacomit	Stiripentol	6 696	8 940	14 354	11 424	16 947	58 360	0.47 %	
Glivec	Imatinib	–	47 731	68 608	–	–	116 340	0.93 %	
Arzerra	Ofatumumab	–	27 830	–	–	–	27 830	0.22 %	
Mozobil	Plerixafor	–	12 796	25 592	–	–	38 389	0.31 %	
Nplate	Romiplostim	–	13 687	–	–	–	13 687	0.11 %	
Revolade	Eltrombopag	–	3 790	–	–	–	3 790	0.03 %	
Tracleer	Bosentan	–	–	–	–	12 697	12 697	0.10 %	

Table 2.9 continued

Trade name	Active substance	Expenditure (EUR)						Share of total expend.	Reimb. category
		2010	2011	2012	2013	2014	Total		
Glivec	Imatinib	1 373 374	1 481 110	1 252 280	–	–	4 106 764	32.94 %	List A (previously List C)
Sprycel	Dasatinib	–	202 997	296 703	412 538	524 119	1 436 357	11.52 %	List C
Tasigna	Nilotinib	–	–	149 561	275 615	285 964	711 140	5.70 %	
Wilzin	Zinc	–	–	–	–	1 534	1 534	0.01 %	List B
Elaprase	Idursulfase	418 275	501 228	596 232	681 408	707 619	2 904 762	23.30 %	CCUH program
Kuvan	Sapropterin	–	–	173 374	173 374	213 828	560 575	4.50 %	
Cystadane	Betaine	–	–	6 265	6 265	6 416	18 945	0.15 %	
Increlex	Mecasermin	–	–	94 257	93 557	93 820	281 634	2.26 %	
Myozyme	Alglucosidase alpha	–	–	–	–	71 548	71 548	0.57 %	
Votubia	Everolimus	–	–	–	–	34 802	34 802	0.28 %	

Table 2.10

Total budget impact of orphan drugs (01.2010–12.2014)

Category of drug expenditure	Expenditure (EUR)					
	2010	**2011**	**2012**	**2013**	**2014**	**Total**
All orphan drugs	2 064 981	2 550 574	3 064 669	2 144 887	2 641 727	12 466 838
Total pharmaceutical market	276 690 000	290 190 000	295 480 000	307 590 000	316 040 000	*Average*
Share of total pharmaceutical market	0.75 %	0.88 %	1.04 %	0.70 %	0.84 %	0.84 %
Total drug reimbursement budget	105 911 722	118 204 402	117 007 689	117 384 880	122 326 421	*Average*
Share of total drug reimbursement	1.95 %	2.16 %	2.62 %	1.83 %	2.16 %	2.14 %

If *Glivec* was excluded from the study, the orphan drug expenditure would increase constantly, from *EUR* 0.692 million to *EUR* 2.642 million (Figure 2.9). It corresponds to more than a threefold increase, from 0.25 % to 0.84 % of the total pharmaceutical market within 5 years.

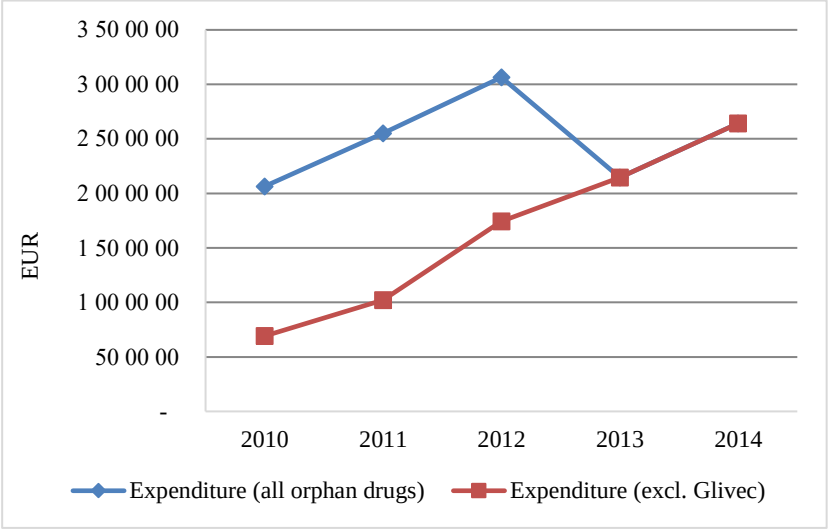

Figure 2.9. **Orphan drug expenditure (01.2010–12.2014)**

In a 5-year period, number of patients receiving orphan drugs increased by 60 %, from 80 to 128 patients. It changed in a similar manner as the orphan drug expenditure, depending on *Glivec* exclusion (Figure 2.10). Until 2012, *Glivec* had the highest annual number of patients, varying between 40 % and 56 % of all patients in 2010–2012, whereas *Revatio* had the highest growth in the number of patients, with more than a fourfold increase within 5 years (from 18 to 77 patients, i.e. 60 % of all patients in 2014). The average overall annual expenditure per patient decreased by 20 %, from *EUR* 25 812 to *EUR* 20 638.

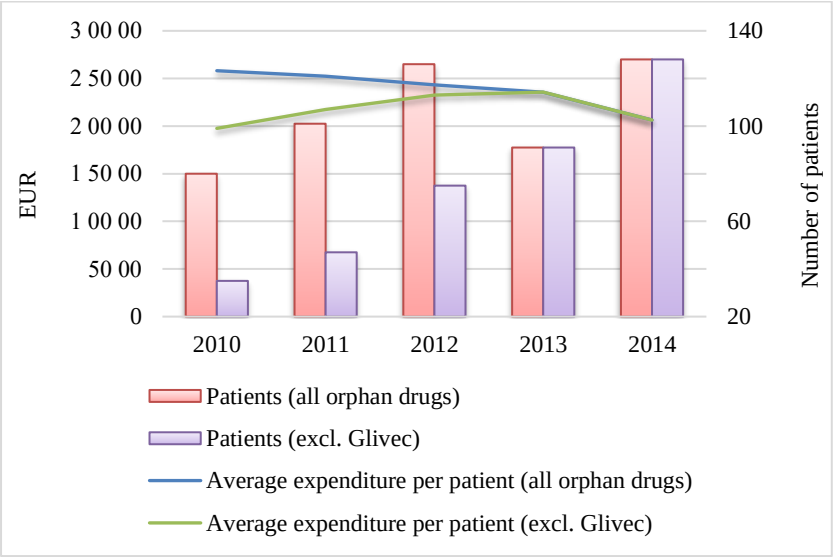

Figure 2.10. **Number of patients and average annual expenditure per patient (01.2010–12.2014)**

Average annual per patient expenditures varied widely, from *EUR* 1 534 for *Wilzin* to *EUR* 580 952 for *Elaprase*, and averaged at *EUR* 23 701 (Table 2.11). Annual budget for *Elaprase* grew constantly, with a peak per patient expenditure reaching *EUR* 707 619 in 2014.

Table 2.11

Average annual expenditure per patient (01.2010–12.2014)

Trade name	Active substance	Average annual expenditure per patient (EUR)
Glivec	Imatinib	30 420; 7 756*
Sprycel	Dasatinib	49 530; 60 450*
Tasigna	Nilotinib	47 409
Wilzin	Zinc	1 534; 495*
Mozobil	Plerixafor	12 796
Nplate	Romiplostim	13 687
Elaprase	Idursulfase	580 952
Myozyme	Alglucosidase alfa	71 548

Table 2.11 continued

Trade name	Active substance	Average annual expenditure per patient (EUR)
Increlex	Mecasermin	40 233
Kuvan	Sapropterin	43 121
Votubia	Everolimus	34 802
Cystadane	Betaine	6 315; 3 432*
Revatio	Sildenafil	6 185
Volibris	Ambrisentan	10 434
Tracleer	Bosentan	12 697
Diacomit	Stiripentol	7 295
Arzerra	Ofatumumab	13 915
Atriance	Nelarabine	12 386
Nexavar	Sorafenib	10 535
Exjade	Deferasirox	6 527
Revolade	Eltrombopag	3 790

* Indicates the individual reimbursement, if a drug was provided through multiple reimbursement mechanisms.

More than a half of the total orphan drug expenditure within 5 years was the expenditure related to two medications, *Glivec* (33.9 %) and *Elaprase* (23.3 %) (Figure 2.11). Moreover, considering the fact that *Glivec* was included in the study until the end of 2012, these two products generated 86.8 %, 79.6 %, and 62.6 % in three consecutive years 2010–2012.

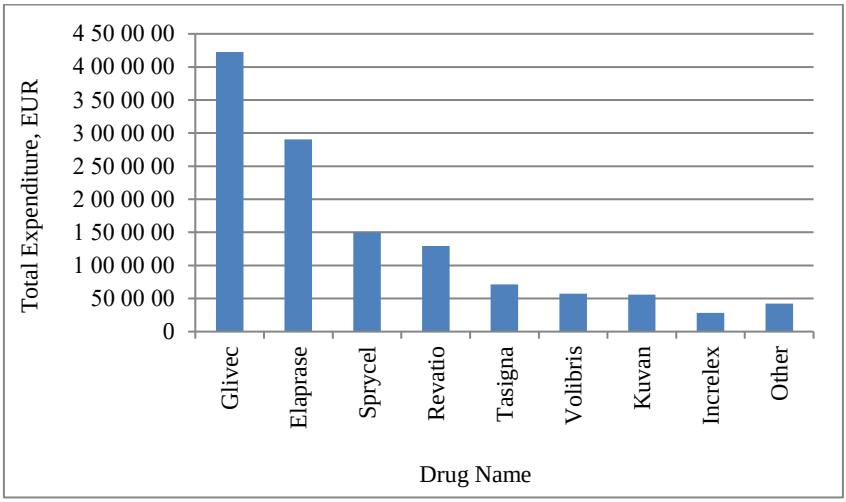

Figure 2.11. **Orphan drugs with the highest total expenditure (01.2010–12.2014)**

Oncology drugs represented 52.99 % of the total orphan drug expenditure, followed by drugs for metabolic and endocrine conditions (30.94 %) and medicines for cardiopulmonary diseases (15.07 %). More specifically, Ph+ CML treatment agents (*Glivec*, *Sprycel*, and *Tasigna*) generated 50.97 % of the total orphan drug expenditure, followed by *Elaprase* for MPS II (23.30 %) and drugs for PAH (*Revatio*, *Volibris*, and *Tracleer*), with 15.07 % (Figure 2.12). Although, these drugs were provided through different reimbursement mechanisms: the total expenditure covering orphan drugs provided through the reimbursement lists was almost exclusively represented by the agents for Ph+ CML (99.98 %), whereas *Elaprase* and drugs for PAH amounted to 75.01 % of the CCUH program and 80.35 % of the individual reimbursement orphan drug expenditures, respectively.

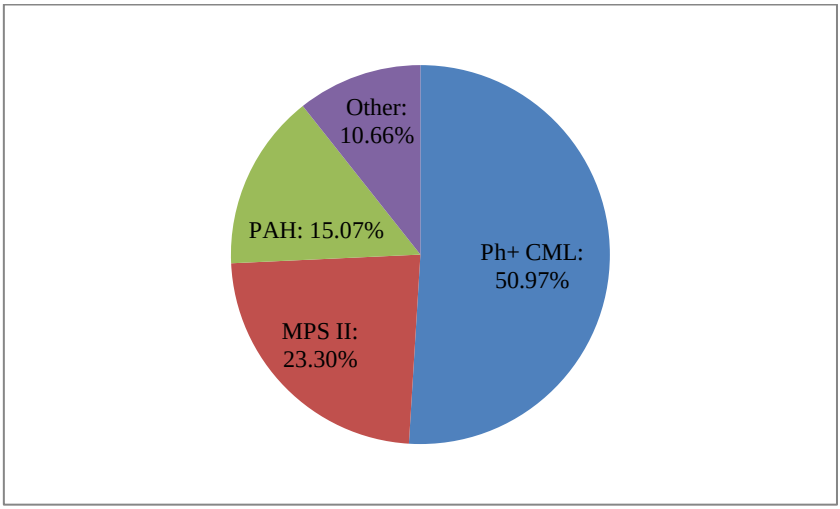

Figure 2.12. **Orphan drug indications with the highest total expenditure (01.2010–12.2014)**

2.5. Comparison with other European countries

Budget impact of orphan drugs as a proportion of the total pharmaceutical market is 3–5 times smaller in Latvia than in other recently studied (in 2012) markets (Table 2.12). Latvian population is 5–40 times smaller and GDP (PPP) per capita is 1.5–2 times smaller than in other countries. Consequently, the orphan drug expenditure per 100 000 inhabitants is 2–12 times smaller in Latvia. This difference is remarkable, considering the time lag between the studies and the different number of orphan drugs authorized in the EU (44 orphan drugs in 2007 vs. 78 in 2014). For example, more than a million *EUR* was spent per 100 000 inhabitants in three countries in 2012, when the number of orphan drugs on the market was closer to the number seen in 2014.

Table 2.12

Budget impact of orphan drugs in European countries

Country (authors and year of the study)	**Budget impact of OD relative to the total drug expenditure**	**Budget impact of OD (million EUR)**	**Year**	**Number of OD with active MA in the EU***	**Population (million)*** (World Bank, 2016b)	**GDP (PPP) per capita*** (World Bank, 2016a)	**OD expenditure per 100 000 inhabitants (EUR)***
UK (Orofino et al., 2010)	1.0 %	162.0	2007	44	61.32	37 507	264 188
Italy (Orofino et al., 2010)	1.5 %	235.5	2007	44	58.44	33 731	402 977
Spain (Orofino et al., 2010)	2.0 %	256.0	2007	44	45.23	32 807	565 996
Germany (Orofino et al., 2010)	2.1 %	525.0	2007	44	82.27	36 782	638 143
Belgium (Denis et al., 2010b)	1.9 %	66.2	2008	49	10.71	37 847	618 114

Table 2.12 continued

Country (authors and year of the study)	**Budget impact of OD relative to the total drug expenditure**	**Budget impact of OD (million EUR)**	**Year**	**Number of OD with active MA in the EU***	**Population (million)*** (World Bank, 2016b)	**GDP (PPP) per capita*** (World Bank, 2016a)	**OD expenditure per 100 000 inhabitants (EUR)***
Netherlands (Kanters, Steenhoek and Hakkaart, 2014)	4.2 %	260.4	2012	64	16.75	46 379	1 554 627
France (Hutchings et al., 2014)	3.1 %	1054.0	2012	64	65.64	37 256	1 605 728
Sweden (Hutchings et al., 2014)	2.5 %	107.2	2012	64	9.52	43 869	1 126 050
Latvia	0.84 %	2.64	2014	78	1.99	22 873	132 663

OD – orphan drugs, MA – marketing authorization, GDP (PPP) per capita – gross domestic product per capita based on purchasing power parity.
* The year covered by a particular study, not the year the corresponding study was published.

A study by *Picavet et al.* (2012) included Latvia in the European analysis of orphan drug market uptake. Latvia was clustered with Hungary and Poland, as countries with a low GDP and a formal HTA organization. This cluster had the lowest orphan drug market volumes and sales. Moreover, in Latvia, only *EUR* 8 000 was spent per 100 000 inhabitants on orphan medicines, compared to approximately *EUR* 560 000 in France. The share of orphan drug sales relative to the total drug market sales varied from 0.07 % in Latvia to 1.90 % in Estonia. These results are critical for Latvia. However, there are some details that should be clarified here. Only 17 orphan drugs were included in the analysis, out of which only five drugs were launched in Latvia. Moreover, orphan drugs which generated the highest expenditures in our study (*Glivec*, *Elaprase*, and *Revatio*) were not included. Therefore, the real market uptake of all orphan drugs authorized in the EU is much higher, although it relates to all European markets, rather than specifically to Latvia. The current study found that the orphan drug expenditure constituted, on average, 0.84 % of the total pharmaceutical market in Latvia. It increased very slightly over a period of five years, remaining under the 1 % threshold, due to the slight increase in the number of patients and the number of orphan drugs reimbursed, whereas the average annual expenditure per patient decreased. In contrast, in the Netherlands, budget impact of orphan drugs increased almost fourfold over a period of six years (Kanters, Steenhoek and Hakkaart, 2014), while both, the number of patients and the number of orphan drugs, almost quadrupled.

Orphan drug expenditures in Latvia are characterized by extremely small numbers, considering a trend of orphan drug budget impact to increase, due to the growing number of orphan medicinal products on the market and the growing number of patients taking these, usually expensive, products. Similar figures were reported only in the very first budget impact studies, when the number of orphan drugs on the European market was small. Thus, orphan medicinal

products accounted for 0.7 % and 1 % of total drug budgets in France and the Netherlands in 2004 (De Varax, Letellier and Börtlein, 2004), when only 15 orphan drugs were authorized in the EU. More recent analyses showed greater impact of orphan drugs on total pharmaceutical market. For instance, the share of total pharmaceutical expenditure spent on orphan drugs in the Netherlands increased markedly, from 1.1 % in 2006 to 4.2 % in 2012 (Kanters, Steenhoek and Hakkaart, 2014). A study of five European countries, with the highest drug expenditure, found that the average overall impact of orphan drugs was 1.7 % of total drug spending in 2007 (Orofino et al., 2010). In Belgium, orphan drugs accounted for 1.9 % of total drug expenditure in 2008 (Denis et al., 2009, 2010b), and it was estimated to grow to about 4 % in 2013. It should be noted that less than 50 orphan drugs had European marketing authorizations at the time of these two studies, in 2007–2008. Later, *Schey, Milanova and Hutchings* (2011) predicted the impact of orphan drugs to increase from 3.3 % of the total European pharmaceutical market in 2010 to a peak of 4.6 % in 2016. Finally, in 2012, budget impact of orphan medicinal products accounted for 2.5 % of total pharmaceutical market in Sweden and 3.1 % in France (Hutchings et al., 2014). These budget impact analyses focused predominantly on the old EU countries with a high GDP. The current study demonstrated that budget impact of orphan drugs in Latvia, as a small Eastern European country with a low GDP and, hence, healthcare budget constraints, is considerably lower. It is, however, complicated to compare the budget impacts of orphan medicines in different countries due to a lack of country-specific epidemiological data for orphan diseases, differences in pricing and reimbursement systems, and time lag between the studies.

Different studies used different approaches and sources of information for the analyses, such as the estimates of budget impact submitted by pharmaceutical companies in the original reimbursement files (or revision files submitted later, when more recent information is available), data published by the HTA

organizations, NHS or other payers, and IMS (Intercontinental Medical Statistics) Health data. The IMS Health database is widely used to evaluate and compare drug markets. Though, it has been pointed out that there are some differences in data quality between countries (Picavet et al., 2012). Moreover, real utilization of medicines may differ from that reflected in sales data. There are both, retrospective and forecasting, types of budget impact analyses. Actual data are used as a basis for forecasts, while forecasting nature of the analyses usually leaves much uncertainty, depending on multiple variables, such as number of orphan designations and marketing authorizations, drug costs, number of patients, reimbursement decisions, availability of therapeutic alternatives, and competition after expiration of marketing exclusivity and patent protection. Budget impact analyses have been criticized for their simplicity (Denis et al., 2009, 2010b, 2011). The analyses are generally limited to evaluating the impact of drug costs, rather than total treatment costs. If an orphan drug has multiple indications, budget impact across all indications is often not considered, likewise the potential savings, if there is alternative treatment available.

3. DISCUSSION

Development of the national plan for rare diseases seems to be an important initial step towards improving situation in this field in Latvia. However, there are currently no official designated centers of expertise as well as no specific register for rare diseases, making it impossible to fully collect and evaluate information on rare diseases. Newborn screening for only two rare disorders is certainly not sufficient resulting in recent discussions concerning expanding of the screening by using tandem mass spectrometry method. The situation appears to be similar in other Baltic States. Lithuanian national plan for rare diseases was approved in 2012 (Rodwell and Aymé, 2014) and it was the first plan in Baltic region. Estonian plan was finalized and submitted to national authorities in 2013. Lithuania and Estonia are among those countries with a low neonatal screening coverage. Neonatal screening programs are currently implemented only for phenylketonuria and congenital hypothyroidism. There are also plans to expand screening and introduce tandem mass spectrometry analysis in both countries. There are currently no official designated centers of expertise for rare diseases in all Baltic States. Some centers are recognized by reputation only. Latvia and Lithuania have plans to designate centers of expertise for rare diseases in the future, while Estonia has no such plans. Similarly to Latvia, Lithuania is planning to implement the e-health information system and establish electronic platform based disease registers (including rare diseases). In Estonia, all health related information is already collected in the electronic health information system, which can be updated and used to extract statistical data about rare diseases.

It has been found that even in such small country as Latvia there are some regional differences in availability of diagnostics, treatment and rehabilitation services for some rare diseases, since university hospitals, scientific and research

institutions are concentrated in the capital and the largest city of Riga. There are also differences in availability of health care services between paediatric and adult patient groups, giving that some orphan drugs were provided solely within the CCUH program. Patient organizations play an important role in increasing awareness and providing necessary pressure on society and policy makers. Several patient organizations support patients and represent their interests, including the Latvian Alliance for Rare Diseases. Public awareness is also supported via Orphanet national website.

According to Lithuanian study published in 2008, shortly after joining the EU, the number of clinical trials aimed at orphan drugs remained low in the Baltic States (Spokiene, 2008). Between May 2004 and June 2007, four clinical trials on orphan medicinal products were approved in Lithuania, one trial in Estonia, and no trials in Latvia. The current study covered a period of time between May 2004 and May 2016 and included both orphan drugs and non-orphan drugs for rare diseases. As a result, 51 clinical trials in rare diseases were identified in Latvia. More than half of them (28 trials) involved orphan medicinal products, indicating that the number of clinical trials for orphan drugs has notably increased in recent years. It should be pointed out, however, that the principal investigators of all of the studies described in the current analysis were not from Latvia, but centers in our country provided sites/ patients to these trials. In fact, none of the trial sponsors was from Latvia or other Baltic States. This applied to both, clinical trials in rare and non-rare diseases, which were almost exclusively sponsored by global commercial pharmaceutical companies. There was only one non-commercial sponsor in each group.

The majority of rare disease clinical studies were phase III studies, while oncology was the biggest therapeutic area, followed by infections and endocrine and metabolic diseases. Oncological conditions and metabolic and endocrine disorders are generally the main indications of orphan drugs (Logviss, Krievins

and Purvina, 2016; Meekings, Williams and Arrowsmith, 2012). The finding that infectious diseases made the second largest therapeutic area in our study can be explained by the fact that MDR-TB was the most studied condition. In fact, the three Baltic States are classified as MDR-TB high burden (high priority) countries with the highest prevalence of MDR-TB in the EU/EEA (ECDC and WHO, 2016). In addition, these countries have established high quality surveillance systems to monitor drug resistance. Disease prevalence as well as diagnostic and treatment options of rare diseases may vary between different EU countries. In this context, conducting clinical studies in MDR-TB in the Baltic States seems rational, as appropriate patients are concentrated there in relatively high numbers.

Conduct of clinical studies in rare conditions may be constrained by the disease prevalence, and studies enrolling several hundred patients may not be practical or possible (Cassino et al., 2013; EMA, 2006). Pivotal clinical trials for rare diseases must meet the same standards of evidence as those for more common conditions, although limitations on patient recruitment should be taken into account (Abrahamyan et al., 2014; Griggs et al., 2009). High quality clinical evidence in drug development comes from well-designed controlled trials with minimized bias through appropriate randomization and blinding. In fact, most orphan drugs approved so far were based on RCT that followed generally accepted rules and standards (EMA, 2006). However, the recruitment challenges have led to the need for development of alternative clinical trial designs and statistical approaches adapted to optimize data from small populations (Buckley, 2008; Griggs et al., 2009). There are a number of alternative trial designs that generally minimize the sample size requirements and maximize the number of patients receiving active treatment (Gagne et al., 2014). Each design has specific advantages and limitations complicating the most appropriate choice (Cornu et al., 2013). Widely described innovative study design options include factorial,

sequential, cross-over, response-adaptive designs, and n-of-1 trials (Abrahamyan et al., 2014; Cornu et al., 2013; EMA, 2006; Gagne et al., 2014; Griggs et al., 2009). Bayesian statistical approaches may also reduce sample size requirements by combining prior information (external or historical data) with the actual trial data.

Efficacy and safety profiles of orphan drugs are often lacking (Joppi, Bertele and Garattini, 2009, 2013). It is difficult to establish effectiveness of a novel rare disease drug, but establishing its safety profile and detection of possible adverse effects may be even more challenging, due to the small numbers of patients and limited exposure (Buckley, 2008; Cassino et al., 2013; Picavet et al., 2013). Therefore, post-marketing surveillance is essential for collection and assessment of long-term safety data. Additionally, rare disease patient registers may help to gather more clinical data and evaluate effectiveness and safety of orphan therapies (EMA, 2006; Picavet et al., 2013; Winstone et al., 2015).

Our findings are consistent with the previous studies reporting that RCT are available for approximately 60 % of rare disease therapies (Joppi, Bertele and Garattini, 2009, 2013; Kanters et al., 2013; Picavet et al., 2013; Winstone et al., 2015) and that significant differences exist in enrollment, randomization, blinding, and the use of active comparators between clinical trials in rare and non-rare conditions (Bell and Tudur Smith, 2014; Dupont and Van Wilder, 2011; Kesselheim, Myers and Avorn, 2011; Mitsumoto et al., 2009; Winstone et al., 2015). As might be expected, clinical trials in rare diseases recruited fewer participants. This is in line with the recent investigation by *Hee et al.* (2017), who examined the association between the disease prevalence and sample size for interventional clinical trials in rare diseases and found that trials of rarer diseases were noticeably smaller than the less rare diseases trials (generally sample size increases as prevalence increases). The authors were surprised that a majority of trials were conducted in one country only, regardless of the disease

prevalence, given the opportunity to recruit more patients in multinational studies. Although, *Bell and Tudur Smith* (2014) found that a higher proportion of rare disease trials were multicenter and multinational studies compared to non-rare disease studies. In the current analysis, all clinical trials were multinational studies involving multiple EEA member states and/ or being conducted both within and outside the EEA. One might logically expect longer trials in rare diseases, as found by *Bell and Tudur Smith* (2014), to compensate for few participants in order to demonstrate statistical significance, but this was not confirmed in the current study. One might also expect more sophisticated statistical modeling, which does not seem to be true empirically. *Unkel et al.* (2016) reviewed the methods used to evaluate therapies in two rare conditions (paediatric multiple sclerosis and Creutzfeldt-Jakob disease) and found that the statistical methodology used was fairly basic. This applied in particular to paediatric multiple sclerosis, for which the evidence on therapeutic interventions was almost exclusively based on observational studies. Studies of this type might have special importance for rare diseases, as large sample size is not readily available for trials in these conditions (Abrahamyan et al., 2014; Gagne et al., 2014; Kanters et al., 2013), though observational studies were out of the scope of the current analysis, which was aimed at interventional studies only. Using the active comparators instead of placebo (which is sometimes unethical), shortening the time patients are on control treatment or placebo, and providing the access to investigational treatment after the study (in open label extensions) may enhance patient enrollment (Abrahamyan et al., 2014) in interventional clinical trials.

The current study has certain limitations. Firstly, we analyzed all (completed and ongoing) interventional clinical trials related to all rare diseases and orphan drugs (authorized and not authorized). In contrast, most previous studies, except the analysis of ClinicalTrials.gov (Bell and Tudur Smith, 2014), were restricted to specific therapeutic areas, such as oncology or neurology, and/

or assessed only pivotal clinical trials (primarily supporting efficacy) of authorized orphan drugs (Kesselheim, Myers and Avorn, 2011; Maeda and Kurokawa, 2015; Mechler et al., 2015; Mitsumoto et al., 2009; Orfali et al., 2012; Picavet et al., 2013; Richey et al., 2009; Winstone et al., 2015). Secondly, this is a register-based study. *Bell and Tudur Smith* (2014) carried out the US register-based analysis of ClinicalTrials.gov (the work extended later by *Hee et al.* (2017), but without comparison between rare and non-rare disease trials), described a number of limitations of the dataset and pointed out that other registers, such as clinicaltrialsregister.eu, can also be used. In the EU Clinical Trials Register, a trial protocol reports the estimated enrollment, rather than the actual number of patients recruited. The expected numbers of patients to be enrolled in clinical trials may be overestimated (Hee et al., 2017). For example, in the above mentioned analysis of ClinicalTrials.gov, the actual enrollment in rare disease trials was 70.1 % of the anticipated enrollment compared to 81.6 % in non-rare disease trials (Bell and Tudur Smith, 2014).

The EU Clinical Trials Register contains information on clinical trials, which started after May 2004, while the orphan drug regulation was introduced in the EU in 2000 (Regulation (EC) No. 141/2000, 2000). Trials started before the implementation of the clinical trial directive in 2004 (Directive 2001/20/EC, 2001) are not listed in the register. Moreover, in March 2011, version 8.0 of the EudraCT database was launched putting in place a more comprehensive set of validation rules for data entry. Historical data, entered into the database between May 2004 and March 2011, may be incomplete or contain inconsistencies, due to less stringent requirements for data entry, or absence of some fields in earlier versions of EudraCT. In addition, research and regulatory procedures alter over time. Potentially less rigorous evaluation criteria might have been used for older therapies than for recently approved ones. Information can also be missing because data have not been provided by the sponsor. However, these limitations

seem to apply equally to both, rare and non-rare disease clinical trials, and are not likely to cause a bias.

The results (outcomes) of clinical trials (drug efficacy and safety) were not analyzed in the current study. Only the design of clinical trials was analyzed, since not all clinical trials have results or summary reports (synopsis) available in the EudraCT database. The lack of information on the results of clinical trials is not unique to rare diseases, the results are not always reported also for common diseases. It is expected that with the entry into force of the new EU clinical trial regulation (Regulation (EU) No. 536/2014, 2014) reporting of clinical trial results will be improved and more detailed analysis will be possible.

According to *Picavet et al.* (2011) orphan designated drugs have higher median price (*EUR* 138.56) than non-designated drugs (*EUR* 16.55) for rare disease indications. Moreover, price of an orphan drug is higher for a disease with a lower prevalence (De Varax, Letellier and Börtlein, 2004). Although, orphan drugs with an alternative have lower annual cost per patient than those without an alternative (Simoens, 2011). Pharmaceutical companies have to comply with different pricing and reimbursement approaches in each EU country, thereby raising the price of orphan drugs (Boon and Moors, 2008). Moreover, prices of drugs distributed through the hospital pharmacies are not regulated in most European countries, but are negotiated directly between the manufacturer and the hospital. According to *Simoens* (2011), there is a need for a transparent and evidence based approach towards pricing and reimbursement of orphan drugs.

Orphan medicines are distributed by both hospital and community pharmacies in Latvia. As of April 2014, 34 orphan drugs were available, including 6 drugs that are no longer considered to be orphan medicines in the EU, concluding that majority of orphan drugs authorized in the EU were not available in Latvia. Orphan medicinal products are partially accessible via the

reimbursement system, with only three drugs included in the positive reimbursement list, all indicated for Ph+ CML. Another pathway for getting orphan drugs is individual reimbursement, with limitation up to *EUR* 14 229 per patient per year. Fifteen orphan medicinal products were provided within this program. Annual limit of *EUR* 14 229 per patient is certainly not sufficient, considering the high prices of orphan drugs. Therefore, treatment costs often exceed this limit and the rest of expenses not covered by the NHS should be paid by the patient or provided by the manufacturer. The situation with access to orphan drugs has even worsened with recent changes in terms and conditions of new regulation on the individual reimbursement making some orphan drugs practically inaccessible for patients. Another significant issue is lack of standard procedure (regulation) for registration and reimbursement of special nutrition and medical foods.

Our study indicated that majority of orphan drugs associated with surgery are used in oncology field. In addition, the only drug included in the reimbursement list (imatinib) is indicated for treatment of different kinds of cancer. However, this finding is not specific for orphan drugs related to surgery. Survey conducted by the Eurordis in 2010 found that rare oncological conditions represented 38 % of authorized orphan medicines and 56 % of patients potentially treated with these medicines (Le Cam, 2010). Similar results were reported by *Schey, Milanova and Hutchings* (2011) stating that, within the total budget impact, 40 % of the conditions, for which orphan drugs were marketed, were oncological and hematological diseases, accounting for 57 % of the total costs in 2010. Thus, oncology is the biggest therapeutic area for orphan drugs as entire group, although the range of orphan indications is dynamic and it is continuously enlarging its field covered by orphan drugs. Historically orphan indications were focused mostly on congenital, metabolic, oncologic, and hematologic diseases, but currently there is a tendency showing that new

indications recognized in medical society appear, including those associated with surgery, that are covered by orphan definition. For example, medicines for treatment of complications consequencing organ transplantation and cardiac surgery. A range of surgical indications could be considerably changed in the future by the advanced therapies and cell therapies studied recently.

Availability and accessibility of orphan drugs in a particular country depend on multiple factors, such as marketing strategy of pharmaceutical companies, market attractiveness, pricing and reimbursement policies. Orphan drugs can be reimbursed through the three main mechanisms in Latvia: the reimbursement list, the individual reimbursement, and the CCUH program "Medicinal treatment for children with rare diseases". The national reimbursement list consists of three parts (Ministru kabineta noteikumi Nr. 899, 2006): List A covers therapeutically equivalent drugs (generics); List B consists of medicines without therapeutic equivalents; and List C contains expensive drugs, for which the annual costs exceed *EUR* 4 269 (previously *LVL* 3 000) per patient, and the manufacturer is obliged to cover treatment expenses (not less than 10 %) for a certain number of patients. This provision is an important tool to manage the costs of expensive medicines, although it is not intended specifically for orphan drugs. For example, *Glivec* was additionally covered by the company for five patients in 2010 (Veselības ekonomikas centra lēmums Nr. 995, 2009) and 2011 (Veselības ekonomikas centra lēmums Nr. 686, 2010). Orphan drugs are usually included in the List C. Starting from 2014, some orphan drugs are also included in the List B (Table 2.5). The individual reimbursement can be provided only if a disease is not included in the reimbursement list, or the disease is included in the list, but there are no drugs included in the reimbursement list for treatment of this condition. Not more than 2 % of the national drug reimbursement budget is intended to the individual reimbursement, with a limitation up to *EUR* 14 229 (previously *LVL* 10 000) per patient per year.

Orphan drugs reimbursed in Latvia can be divided in two groups. Drugs provided through the reimbursement lists and the CCUH program can generally be considered fully accessible to patients, whereas drugs provided through the individual reimbursement are frequently only partially accessible, considering the annual limit of *EUR* 14 229 per patient. This threshold is too low. Only *Revatio*, *Diacomit*, *Cystadane*, *Wilzin*, and *Mozobil* can be fully provided within this limit. Other orphan drugs should be additionally covered by the manufacturers, charities or patients themselves.

Number of orphan medicines reimbursed per year through the three reimbursement pathways increased slightly, reaching 15 drugs in 2014. It is less than 20 % out of 78 orphan drugs with active marketing authorizations in the EU in the same year. The remaining drugs are practically inaccessible to rare disease patients. Decisions to launch the product on the market and to apply for the reimbursement are taken by the manufacturer. Market size plays a crucial role in these decisions. The absolute number of rare disease patients treated in Latvia is very low. Some orphan drugs (including *Elaprase*) were reimbursed for a single patient. There might be no diagnosed patients eligible for the treatment with a particular orphan drug. In 2014, a total of 128 patients received orphan drugs in Latvia. In contrast, in the Netherlands, *Glivec* alone was provided to 1 485 patients in 2012 (Kanters, Steenhoek and Hakkaart, 2014). The low number of patients along with the fiscal constraints make Latvian market less attractive for the manufacturers of orphan drugs.

Orphan drugs are generally less reimbursed in new EU Member States (De Varax, Letellier and Börtlein, 2004), whose health care budgets are considerably lower than those of older Member States. A Bulgarian study reported similar findings, where over two-thirds of orphan drugs were not reimbursed in 2014 (Iskrov and Stefanov, 2014). Authors compared this number with other EU Member States, where about 80 % of orphan medicinal products

were incorporated in the healthcare systems. They also pointed out that time delay from the EU marketing authorization to the positive reimbursement decision is much longer in Bulgaria than in other countries. Bulgaria is bigger country than Latvia, with a population of 7.2 million vs. 2.0 million in Latvia (World Bank, 2016b), and consequently more rare disease patients. According to the Eurordis survey, especially smaller countries suffer from longer delay in availability of orphan medicines (Bignami, 2007). Differences in the annual per patient costs for a given orphan drug can reach 70 % between the EU countries (De Varax, Letellier and Börtlein, 2004). Besides, orphan drug prices are higher in the smaller of new EU Member States, such as the Baltics, than in the bigger states, such as Poland or the Czech Republic.

Oncological drugs represented more than a half of the total orphan drug expenditure, followed by drugs for metabolic and endocrine conditions and medicines for cardiopulmonary diseases. Those are generally the main therapeutic areas of orphan drugs (Denis et al., 2010b; Iskrov and Stefanov, 2014; Meekings, Williams and Arrowsmith, 2012; Orofino et al., 2010). In 2010, oncological and haematological disorders accounted for 57 % of the total orphan drug costs in Europe (Schey, Milanova and Hutchings, 2011). Within these therapeutic areas, there are some indications, for which either multiple orphan drugs or highly expensive orphan drugs are available. Thereby, nearly 90 % of the total orphan drug expenditure in our study covered only three indications: Ph+ CML, MPS II, and PAH. One of such orphan drugs for Ph+ CML treatment, *Glivec*, is a blockbuster anticancer drug with multiple orphan indications. It generated 34 % of the total orphan drug expenditure within 5 years. Similar results were reported in other studies. The majority of orphan drugs have relatively low sales (Hutchings et al., 2014), except few high-cost orphan drugs. For instance, the total sales of *Glivec* reached *EUR* 679 million in the five biggest European countries in 2007 (Orofino et al., 2010). It was more than 40 % of the

total orphan drug expenditure. Moreover, if the expenditures relating to three drugs (including imatinib) with the highest sales were excluded from the study, budget impact of the remaining orphan medicines would be more than halved. In our study, it would be enough to exclude just two medications (*Glivec* and *Elaprase*) to reach similar result. In a Dutch study, *Glivec* also had the highest cumulative budget impact (*EUR* 251.2 million) (Kanters, Steenhoek and Hakkaart 2014). It accounted for 34 % of the total orphan drug expenditure between 2000 and 2012 in Sweden, and 27 % in France (Hutchings et al., 2014).

Loss of intellectual property, such as expiration of marketing exclusivity and patent protection, can greatly affect drug prices and result in an increased competition. As reported by *Onakpoya et al.* (2015), for orphan drugs, where generic alternatives were available, the branded products were from 1.4 to 82 000 times more expensive. However, it is not clear yet whether the orphan drug market is attractive enough for generic companies to enter the field of rare diseases. Orphan drug market has distinctive features, characterized primarily by specific European regulation, small number of patients, and high drug prices. In addition, orphan medicines have remarkably higher proportion of large-molecule than small-molecule agents (Meekings, Williams and Arrowsmith, 2012), compared to non-orphan drugs. Since the biologicals are currently less subjected to generic (biosimilar) competition than the small molecules, they can maintain high economic value even after the patent expiration. The current study demonstrated that generic companies may have a big interest in some orphan drugs. Starting from May 2013, *Glivec* was moved to the reimbursement List A, because generic drugs became available, that changed prescribing and reimbursement criteria for imatinib. In fact, cheaper imatinib generics practically replaced the brand drug from the reimbursement system. In 2014, the reimbursement expenditure covering *Glivec* was only *EUR* 2 904, compared to the annual expenditure varying between *EUR* 1.321 and 1.529 million in 2010–

2012. However, *Glivec* should not be considered as a model for all orphan drugs, since it is a small molecule, used for multiple indications, and known for a long time as a classical blockbuster orphan drug. Not all orphan medicines are expected to cause such interest from the generic companies. It should be noted that orphan drugs were excluded from the analysis when the period of market exclusivity ended. It is likely that these drugs will still have a budgetary impact, as patients will continue using them. However, these products were removed from the Community register of orphan medicinal products and are no longer considered orphan medicines in Europe.

Annual per patient costs can vary broadly between different orphan drugs: *EUR* 1 534–580 952 (current study); *EUR* 6 000–300 000 (De Varax, Letellier and Börtlein, 2004); *EUR* 331–337 501 (Orofino et al., 2010); *EUR* 1 251–407 631 (Schey, Milanova and Hutchings, 2011); *GBP* 726–378 000 (Onakpoya et al., 2015). In the present study, the two most expensive drugs, on the annual per patient basis, were *Elaprase* and *Myozyme*. Both medicines were provided through the CCUH program, as enzyme replacement therapy (ERT) for MPS II and Pompe disease. The program provided ERT also for Gaucher disease (*Cerezyme*) and MPS I (*Aldurazyme*), however these products are not considered orphan drugs in Europe. In fact, if *Cerezyme* and *Aldurazyme* were included in the study, they would be among the most expensive medicines, with the average annual per patient expenditures *EUR* 213 716 and *EUR* 157 248, respectively, and more than *EUR* 1 million of the total expenditure in 5 years.

ERT for Gaucher disease was the most costly per patient therapy in Israel (Kesselman et al., 2006). To decrease the costs authors recommended to apply criteria of disease severity, use low-dose regimen or even “drug vacations”. In Bulgaria, MPS and glycogen storage diseases (conditions treated with ERT) were rare diseases with the highest costs per patient (Iskrov and Stefanov, 2014). *Elaprase* and *Naglazyme* had the highest estimated annual costs among the

inpatient orphan drugs in the Netherlands (Kanters et al., 2013), whereas *Myozyme* had the highest budget impact. However, it appears that ERT is not the most expensive treatment worldwide. *Soliris* (eculizumab), for the treatment of paroxysmal nocturnal haemoglobinuria, was mentioned as the most expensive drug in the world (Meekings, Williams and Arrowsmith, 2012), with annual cost around *USD* 500 000 in 2010. The latest price record was set by *Glybera* (alipogene tiparvovec) (Ylä-Herttuala, 2015), the first gene therapy drug approved by the EMA for lipoprotein lipase deficiency in 2012, with a cost over *EUR* 1 million per patient. Both drugs are designated orphan medicinal products in the EU.

Orphan drug expenditure grew faster (with annual growth rates 20–25 % in the years not affected by the change in the status of *Glivec*) than the total pharmaceutical market (annual growth rates 2–5 %) and the total drug reimbursement budget (Table 3.1). The only negative growth (-30 %) was observed in 2012–2013, that was caused by the change in the status of *Glivec*. Based on the observed trends, it is likely that the budget impact of orphan drugs in Latvia will follow the general European tendencies and will continue to grow in the future, both in absolute numbers and relative to the total pharmaceutical market. This assumption is strengthened by the fact that the number of orphan drugs will only increase in the future, both at European level (14 new orphan drugs were approved by the EMA in 2015) and at Latvian national level (3 orphan drugs were included in the reimbursement list in 2014–2015). Other studies have shown that the budget impact of orphan drugs in European countries is increasing, however the growth rates are decreasing over time (Hutchings et al., 2014; Kanters, Steenhoek and Hakkaart, 2014; Schey, Milanova and Hutchings, 2011), due to expiration of patents and marketing exclusivity of existing orphan drugs. It is, therefore, likely that the budget impact of orphan drugs in Latvia will remain sustainable and relatively small in the long run.

Although, it should be pointed out that currently available data is too limited to create a detailed and well validated model for the reliable forecast of the future budget impact of orphan drugs in Latvia. Further research is needed to identify the trends of orphan drugs, including the detailed information on the availability and accessibility of orphan drugs (including the time lag between the orphan drug marketing approval in the EU and the inclusion in the reimbursement system in Latvia), the potential patient population, and the prices of orphan drugs.

Table 3.1

Annual growth rates (01.2010–12.2014)

Expenditure	2010–2011	2011–2012	2012–2013	2013–2014
Orphan drugs (all)	23.52 %	20.16 %	–30.01 %	23.16 %
Orphan drugs (excl. *Glivec*)	47.73 %	70.67 %	23.00 %	23.16 %
Total pharmaceutical market	4.88 %	1.82 %	4.10 %	2.75 %
Total drug reimbursement budget	11.61 %	–1.01 %	0.32 %	4.21 %

The issue of the availability of medicinal products to rare disease patients remains unresolved, since the evaluation of orphan drugs to be included in the national reimbursement drug list is subject to the same clinical and economic evaluation criteria as other medicines (Ministru kabineta rīkojums Nr. 602, 2017). The assessment of cost-effectiveness (*EUR* 41 000 per extra year of life gained or year of life without disease progression) and impact on the drug reimbursement system budget is the same for all medicines. The new national plan states that orphan drugs were reimbursed for a total of *EUR* 2.5 million through the all three reimbursement pathways in 2016, which is in line with the results of the current study for 2010–2014, when the overall orphan drug expenditures were between *EUR* 2.065 and 3.065 million per year (*EUR* 2.493 million on average).

A limitation of the current study is, in fact, that the annual per patient expenditures were estimated from the payer's (NHS) perspective only. For drugs provided within the individual reimbursement system, the actual drug costs may be much higher, considering the limit of *EUR* 14 229 per patient per year covered by the NHS. If the drug cost exceeds this limit, the rest of expenses should be covered by the manufacturers, charities or patients. Information concerning the expenses not covered by the NHS is not publicly available, although it should not have direct impact on Latvian healthcare budget. Thus, for orphan drugs reimbursed individually, the annual per patient expenditures may be considered as the actual drug costs, only if the above mentioned limit was not exceeded, i.e. for *Revatio*, *Diacomit*, *Cystadane*, *Wilzin*, and *Mozobil*.

Another limitation of our study can be found in the different approach for estimating the number of patients receiving particular drugs. For the individual reimbursement and the CCUH program, this number was known from the NHS reports, while for orphan drugs included in one of the reimbursement lists, the number of drug packages reimbursed by the NHS was known instead. To estimate the number of patients receiving such drugs we considered the recommended maintenance daily doses used for the main indications in adults. Therefore, the estimated number of patients for *Sprycel* and *Tasigna* (indicated in adults only) could be closer to the actual number of patients than for *Glivec* and *Wilzin*, which are indicated in both, adult and pediatric patients. It should be noted that not all patients are treated for a whole year and with the recommended maintenance doses. Additionally, for drugs used for Ph+ CML treatment, the main indication was considered Ph+ CML in chronic phase, rather than accelerated or blast phases.

Denis et al. (2010a) compared rare disease and orphan drug markets in six European countries. France, Italy, Sweden and UK have dedicated centers of reference for rare diseases. Besides, there are no official centers of reference in

Belgium and the Netherlands, but several medical centers fulfill this role. France, Italy and the Netherlands have implemented additional policy measures and research incentives to promote research and development of orphan medicines. Marketing authorization of orphan drugs is responsibility of the EU, but France has a domestic procedure in place for authorization of orphan products (for temporary use before getting approval from the EMA). There are programs for compassionate use of orphan drugs in Belgium, France, Italy, the Netherlands, and UK, but there is no legislation governing compassionate use in Sweden. Some similarities and differences can be found when comparing Latvian situation with the above mentioned European countries. For example, there are no official centers of reference in Latvia, but several medical centers fulfill this role, similarly to the process in Belgium and the Netherlands. Generally some funding is available for rare diseases and several research projects take place in Latvia, although these funds and incentives are not specifically designed for rare disease research. As in most EU countries, there is no domestic orphan drug authorization procedure, but several programs for orphan drug compassionate use take place in Latvian hospitals.

Belgium, France, Italy and the Netherlands compare the price of orphan medicine with the price in other countries (Denis et al., 2010a), while Sweden and UK have free pricing system. All countries included in the above mentioned study consider the budget impact of orphan drugs in the reimbursement application, except Sweden, whereas cost-effectiveness is considered in all countries, except Belgium. In Latvia, there is no specific policy for the pricing and reimbursement of orphan drugs. The NHS evaluates therapeutic value, price, expected budget impact and cost-effectiveness for each drug before it is included in the reimbursement list. Drug price is compared with prices in the following EU countries: Czech Republic, Denmark, Romania, Slovakia, Hungary, Estonia and Lithuania. Comparison with these mostly smaller Eastern European

countries (excluding Denmark) seems to be very logical taking into consideration geopolitical location of Latvia, lower GDP level, small population and market size. It can be expected that Latvian situation is likely to be closer to these countries.

Some studies in the field of rare diseases conducted in other Eastern and Southern European countries recently came to light. For instance, in Bulgaria, there is no national register or centers of expertise for rare diseases (Iskrov, Miteva-Katrandzhieva and Stefanov, 2012). Regulation of compassionate or off-label use of orphan drugs is also missing. Price of orphan medicines which are going to be included in the reimbursement list is compared with reference prices in a set of EU countries (including Baltic States). Before inclusion in reimbursement list drugs are also assessed for therapeutic value and social significance, but cost-effectiveness of the drug is not considered. The allocation of funds for orphan medicines is made once per year and it is based on the previous year's budget. Neither national register, nor policy measures, and research incentives for rare diseases exist in Serbia (Pavlović et al., 2012). Cost-effectiveness, budget impact, and the need for a given treatment are taken into account when assessing reimbursement application of a drug. Orphan medicinal products are reimbursed from the national health insurance fund, which reimburses only medicines that are registered in Serbia (Rodwell and Aymé, 2014). There is no centralized marketing authorization procedure in place since Serbia is not the EU Member State. Domestic registration is therefore required, that can take additional time and delay patient access to orphan drugs. Compassionate and off-label use is not recognized by the health insurance system in Serbia, although there is a special fund for reimbursement of the treatment of paediatric patients with metabolic diseases requiring enzyme replacement therapy. Around *EUR* 2.6 million was planned for this purpose in 2014.

According to *Denis et al.* (2010a), 31 orphan drugs were marketed in Belgium in 2008; 35 drugs in France in 2007; 23 drugs in Italy in 2007; 40 drugs in the Netherlands in 2008; 28 drugs in Sweden in 2008; and 20 drugs in UK in 2006. The situation on orphan drug reimbursement in the studied countries was as follows: 32 orphan drugs were reimbursed in Belgium (2009); 35 in France (2007); 21 in Italy (2007); 32 in The Netherlands (2009); 28 in Sweden (2008); and 12 in Scotland (2008). The current study was conducted in 2014 and it found that 34 orphan drugs (28 pure orphan products) were available in Latvia, and only three orphan drugs were included in the positive reimbursement list. This number is extremely small, especially considering the time difference between the studies and the growing number of orphan medicinal products. There were 47 orphan drugs on the European market by the end of 2008 (Denis et al., 2010a), while 72 orphan drugs were authorized in the EU in April 2014.

Surveys on orphan drug availability in Europe had pointed out unacceptable delays and inequalities in rare disease patients' access to their medicines. Especially countries with a small population suffer from a longer delay in availability of drugs. In 2007, overall lowest availability of orphan drugs was demonstrated in Estonia and Lithuania (Bignami, 2007). In 2010, the number of patients with potential access to orphan drugs ranged from 34 % in Greece up to 98 % in France (Le Cam, 2010). The price also varied between the countries, and in some countries it was up to 160 % higher than the lowest European price. Another European study found that differences in annual costs per patient between the EU countries for a given orphan drug may reach 70 % (De Varax, Letellier and Börtlein, 2004). Newer EU Member States are often facing budget restrictions with healthcare budgets much lower than compared to older Member States (Michel and Toumi, 2012), thereby reimbursement levels can differ. Thus, the number of available (marketed) orphan drugs in Bulgaria was 22 and 16 of them were accessible (reimbursed) for patients in 2011. *Iskrov, Miteva-*

Katrandzhieva and Stefanov (2012) pointed out that this is an important issue especially for Eastern European countries, as a big part of orphan drugs are not priced and reimbursed in many countries. In this geographical and economical region, the price level of orphan drugs is not among the lowest in the EU, and that could be explained by the small market size represented by these countries. Serbia might be mentioned as another example, where only four orphan medicines were reimbursed (Pavlović et al., 2012). Authors also suggested that GDP value may partly explain the differences in the level of orphan drug reimbursement among the European countries, since Serbia is a country with a low GDP. Baltic States are also among the countries with a low GDP. In Lithuania, budget assigned for reimbursement of orphan medicines is limited and insufficient (*EUR* 1.89 million in 2006) (Spokiene, 2008), therefore access to health care services and orphan drugs in some cases is restricted. 29 orphan medicinal products were marketed in Lithuania in 2011 (Rodwell and Aymé, 2014), and about *EUR* 3 million was allocated for reimbursement of medicinal products and devices for rare diseases in 2013. There is no specific pricing and reimbursement policy for orphan drugs in Estonia. They are reimbursed on the same basis as other medicines. 20 orphan drugs were fully reimbursed by the Estonian health insurance fund. The fund has also reimbursed off-label drugs and medical foods for rare disease patients.

CONCLUSIONS

1) Development and approval of the national plan for rare diseases is an important step towards improving the situation in the field of rare diseases. However, there is still a lot to do and further action is required to improve access to information on rare diseases for both health care professionals and patients. Diagnostics of rare diseases (including newborn screening) also require improvements. Creation of a rare disease patient register and centers of expertise would allow to collect and evaluate information on specific rare diseases, that would greatly improve the current situation and coordination of further activities in the field. Data collected through the register should also be used to assess the long-term effectiveness and cost-effectiveness of orphan medicines and should be harmonized at the EU level. Early detection and prevention of rare diseases, integrated health care for patients, timely access to orphan drugs and continuing education of health care professionals play crucial role in improving quality of life of patients suffering from orphan diseases. Many of these activities are included in the national plan for rare diseases and most of them are currently in the process of development.
2) Quality of clinical evidence is affected by numerous challenges faced by investigational drugs for rare diseases. Despite the fact that RCT are available for over 60 % of rare disease therapies, clinical trials in rare diseases vary from those in non-rare conditions. Clinical studies in orphan diseases enroll fewer participants and are less likely to use randomization, blinding, and active comparators. However, we found no significant difference in trial duration and the use of overall survival as a primary endpoint. All clinical trials included in the analysis were multicenter and

multinational studies highlighting the importance of European and global collaboration in the conduct of clinical studies in small populations.

3) Oncology is the biggest therapeutic area of orphan drugs. However, it is specific for orphan drugs as entire group, rather than for orphan drugs that are exclusively related to surgery. The range of orphan indications is dynamic and it has a tendency showing that new indications recognized in medical society appear, including those associated with surgery, that are covered by orphan definition. For example, medicines for treatment of complications consequencing organ transplantation and cardiac surgery. A range of surgical indications could be considerably changed in the future by the advanced therapies and cell therapies studied recently. In the EU, orphan drugs were approved for surgery related indications also following the period covered by the study (in 2015–2018). For example, *Coagadex* for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency. Relatively often indications of newly approved orphan medicinal products are associated with stem cell transplantation (*Defitelio*, *Prevymis*, *Qarziba*, *Zalmoxis*). However, there is also an opposite trend, when orphan drugs are indicated for use in patients who can not undergo surgical intervention (including inoperable tumors) or in patients for whom surgery has failed (*Adempas*, *Cometriq*, *Lartruvo*, *Lutathera*, *Signifor*, *Votubia*).
4) The majority of orphan drugs authorized in the EU are not available in Latvia, moreover those drugs that are available are often not accessible because they are insufficiently reimbursed by the state, and are too expensive to be covered by patients.
5) Latvia is in a position of “a small market within the small market” or “ultra-small market” for orphan drugs, considering the small population,

low GDP, healthcare budget constraints, and imperfections in drug reimbursement system. Currently, budget impact of orphan drugs in Latvia is very small, compared to other European countries. Orphan drug expenditure is expected to increase in the future, as more orphan drugs will become available, both at European and Latvian level. However, in the long run, the growth rate of the orphan drug expenditure is expected to diminish and level off, as patents and marketing exclusivity of existing orphan drugs will expire. It is, therefore, likely that the budget impact of orphan drugs in Latvia will remain sustainable and relatively small. Patient access to rare disease therapies in Latvia needs to be improved, considering the disease severity and unmet medical needs, while the orphan drug expenditure should be efficiently managed. This is challenging but achievable through enhanced cooperation between all stakeholders and implementation of different reimbursement mechanisms, such as various types of risk-sharing agreements and conditional reimbursement programs, which link the reimbursement to health and economic outcomes. These mechanisms can be combined with rare disease registers and post-marketing surveillance programs that capture clinical and economic data and monitor orphan drug uptake. In this context, international cooperation and European collaboration are of crucial importance.

RECOMMENDATIONS

The author of the current study participated in meetings of the Working group on "The development of the action plan for organization of health care for rare disease patients" (development of the first national plan for rare diseases) held by the Ministry of Health of the Republic of Latvia. To continue the activities initiated in the previous plan (2013–2015) and to anticipate additional funding required for implementation of these activities, a second plan was developed for the period 2017–2020. It has been done in cooperation between the concerned parties: state institutions (MoH, CDPC, NHS), non-governmental organizations (Latvian Alliance for Rare Diseases, Association of Rare Disease Specialists, Human Medical Genetics Association) and specialists in the field of rare diseases (CCUH, PSCUH, RECUH, BMC, RSU, LU). Therefore, the (author's) recommendations of the doctoral thesis largely correspond with the (stakeholders') goals and action directions defined in the national plan for rare diseases (Ministru kabineta rīkojums Nr. 602, 2017). Implementation of these recommendations aimed at improving the early diagnostics, timely treatment and flow of information for rare diseases depends on the financial abilities of the state budget. In order to carry out the activities outlined in the new plan, a total of *EUR* 66.9 million of additional state budget financing is needed for 2018–2020, and further an additional funding of *EUR* 30.5 million will be required annually.

1) To initiate the DNA diagnostics for the pathologies that are relatively common in Latvian population, expand the list of state funded services to cover diseases for which DNA diagnostics affects treatment, prognosis or course of the disease.
2) To improve the availability of genetic tests not only for children but also for adult patients with appropriate indications, including enabling them to receive services in other EU countries.

3) To provide genetic tests for both expectant parents if there is a history of genetic illness or a reasonable suspicion of it.
4) To use the Genome Database of Latvian Population more actively for diagnostics, research, and prognosis of rare diseases, as well as for planning of health care services and for patient biological material and clinical data management.
5) To revise the drug reimbursement system by adding diagnosable rare diseases to a list of state funded conditions, as well as adding medicines for the treatment of rare diseases (including orphan drugs) to a reimbursement drug list and increasing the amount of individual reimbursement.
6) To create a separate program with independent funding for the medicinal treatment of rare diseases in adult patients, as well as to improve the CCUH program "Medicinal treatment for children with rare diseases" and to ensure the continuity of medicinal treatment for patients during their transition from pediatric to adult care.
7) The Baltic States should continue to cooperate (e.g. joint procurement of vaccines), as well as to expand the mutual collaboration and to take the good practices from other EU countries in the field of drug pricing and reimbursement policies (some of the EU countries cooperate on the joint drug price and reimbursement negotiation process in order to reduce the drug costs, including orphan drugs (Government of the Netherlands, 2018)), by jointly negotiating with pharmaceutical companies and agreeing on costs and volumes of medicinal products.
8) To provide the possibility to receive not only drugs but also other health care services and products for rare disease patients, covering the related costs from the state budget, including the reimbursement of special nutrition (medical foods), assistive technologies (e.g. mobility devices and oxygen devices), lung transplantation and pulmonary endarterectomy.

9) To strengthen the expertise of medical practitioners in recognizing rare diseases, involving professionals of different specialties and providing them with appropriate training, including continuing education, conferences, seminars and exchange of experience.
10) To provide the possibility to involve the multidisciplinary teams of specialists in the treatment and care of rare disease patients.
11) To introduce a regular evaluation of clinical efficacy of medications prescribed for rare disease patients according to predefined criteria.
12) To improve the flow of rare disease patients by strengthening the Rare Disease Coordination Center in CCUH and support units in PSCUH and RECUH.
13) To improve the existing patient registers (the Congenital Anomaly Register and the Register of Patients Suffering from Certain Diseases) and the electronic information systems (the e-health system and the management information system) by linking the information contained in different databases. To develop the centralized registration of rare disease patients on the basis of the established joint information platform. The platform should also be used to ensure the follow-up of the health care services and medications prescribed for rare disease patients, as well as to evaluate the effectiveness of the interventions received and to use the obtained statistical data for health care budget planning.
14) To continue the systemic implementation of Orpha codes for rare diseases and congenital anomalies in the health care statistical systems, as well as to link them to the international disease classification codes in order to estimate the number of patients and the prevalence of rare diseases in Latvia.
15) To promote the use of modern IT solutions for the processing of health care data, not only at national but also at the EU level, by integrating data from

databases, registers, biobanks and clinical information into joint platforms (e.g. RD-Connect) in the field of rare diseases.

16) To raise awareness about rare diseases in general public, patients and medical practitioners using a variety of resources available, including the Orphanet database.

REFERENCES

1. Abrahamyan, L., Diamond, I. R., Johnson, S. R. and Feldman, B. M. 2014. A new toolkit for conducting clinical trials in rare disorders. *J Popul Ther Clin Pharmacol*. 21(1), e66–78.
2. Akuličs, S. 2012. Līdzjutības zāļu lietošanas nosacījumi Latvijā. *Cito!* 1(48), 7–9.
3. Aymé, S. and Rodwell, C. 2012. 2012 Report on the state of the art of rare disease activities in Europe of the European Union Committee of experts on rare diseases. *EUCERD*. Available from: http://www.eucerd.eu/?post_type=document&p=1501 [viewed 29.01.2014.].
4. Aymé, S. and Rodwell, C. 2013. 2013 Report on the state of the art of rare disease activities in Europe. *EUCERD*. Available from: http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesLV.pdf [viewed 29.01.2014.].
5. Bell, S. A. and Tudur Smith, C. 2014. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet J Rare Dis*. 9:170.
6. Bērnu klīniskā universitātes slimnīca. 2014. *BKUS*. Iegūts no: http://www.bkus.lv/page/?main_page_id=&page_type=&second_page_id=&news_id=685 [sk. 29.01. 2014.].
7. Bignami, F. 2007. Eurordis survey on orphan drugs availability in Europe. *6th Eur ordis round table of companies workshop*. Barcelona. Available from: http://www.eurordis.org/IMG/pdf/2007ODsurvey-eurordis.pdf [viewed 02.05.2014.].
8. Binns, R. and Driscoll, B. 2000. New European rules on orphan drugs. *Pharm Sci Technol To*. 3(7), 218–219.
9. Boon, W. and Moors, E. 2008. Exploring emerging technologies using metaphors – a study of orphan drugs and pharmacogenomics. *Soc Sci Med*. 66, 1915–1927.
10. Buckley, B. M. 2008. Clinical trials of orphan medicines. *Lancet*. 371, 2051–2055.
11. Cassino, C., Orfali, M., Charnigo, R. J. and Marsden, D. L. 2013. Rare and orphan diseases challenges: clinical development and clinical practice. *J Rare Disord*. 1(1), 1–3.
12. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on rare diseases: Europe's challenges (COM (2008) 679). 2008. *Commission of the European Communities*. Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf [viewed 05.04.2013.].
13. Cornu, C., Kassai, B., Fisch, R., Chiron, C., Alberti, C., Guerrini, R., Rosati, A. et al. 2013. Experimental designs for small randomised clinical trials: an algorithm for choice. *Orphanet J Rare Dis*. 8:48.
14. Council Recommendation (08.06.2009.) on an action in the field of rare diseases (2009/C151/02). 2009. *Offic J Europ Communities*. C151, 7–10.
15. De Varax, A., Letellier, M. and Börtlein, G. 2004. Study on orphan drugs. Phase I: overview of the conditions for marketing orphan drugs in Europe. *Alcimed*. Available from: http://ec.europa.eu/health/files/orphanmp/doc/pricestudy/final_final_report_part_1_web_en.pdf [viewed 08.12.2015.].

16. Denis, A., Mergaert, L., Fostier, C., Cleemput, I. and Simoens, S. 2010a. A comparative study of European rare disease and orphan drug markets. *Health Policy*. 97, 173–179.
17. Denis, A., Mergaert, L., Fostier, C., Cleemput, I. and Simoens, S. 2010b. Budget impact analysis of orphan drugs in Belgium: estimates from 2008 to 2013. *J Med Econ*. 13(2), 295–301.
18. Denis, A., Mergaert, L., Fostier, C., Cleemput, I., Hulstaert, F. and Simoens, S. 2011. Critical assessment of Belgian reimbursement dossiers of orphan drugs. *Pharmacoeconomics*. 29(10), 883–893.
19. Denis, A., Simoens, S., Fostier, C., Mergaert, L. and Cleemput, I. 2009. Policies for orphan diseases and orphan drugs. *Health Technology Assessment (HTA). Belgian Health Care Knowledge Centre (KCE).* KCE reports 112C (D/2009/10.273/32). Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/policies_orphan_en.pdf [viewed 08.12.2015.].
20. Directive 2001/20/EC of the European Parliament and of the Council (04.04.2001.) on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001. *Off J Eur Communities*. L121, 34–44.
21. Drummond, M. F., Wilson, D. A., Kanavos, P., Ubel, P. and Rovira, J. 2007. Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess Health Care*. 23(1), 36–42.
22. Dupont, A. G. and Van Wilder, P. B. 2011. Access to orphan drugs despite poor quality of clinical evidence. *Br J Clin Pharmacol*. 71(4), 488–496.
23. European Centre for Disease Prevention and Control (ECDC) and WHO Regional Office for Europe. 2016. Tuberculosis surveillance and monitoring in Europe 2016. Surveillance report. *ECDC*. Available from: http://ecdc.europa.eu/en/publications/Publications/ecdc-tuberculosis-surveillance-monitoring-Europe-2016.pdf [viewed 21.02.2017.].
24. European Commission. 2005. Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. *European Commission*. Available from: http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf [viewed 29.01.2014.].
25. European Commission. 2015. European Community Register of designated orphan medicinal products. *European Commission*. Available from: http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm [viewed 08.12.2015.].
26. European Medicines Agency (EMA). 2001. Choice of control group in clinical trials. ICH topic E10. CPMP/ICH/364/96. *EMA*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf [viewed 08.07.2016.].
27. European Medicines Agency (EMA). 2006. Guideline on clinical trials in small populations. CHMP/EWP/83561/2005. *EMA*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf [viewed 08.07.2016.].
28. European Medicines Agency (EMA). 2015. Rare disease (orphan) designations. *EMA*. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&mid=WC0b01ac058001d12b [viewed 8.12.2015].

29. Gagne, J. J., Thompson, L., O'Keefe, K. and Kesselheim, A. S. 2014. Innovative research methods for studying treatments for rare diseases: methodological review. *BMJ*. 349:g6802.
30. Gatta, G., van der Zwan, J. M., Casali, P. G., Siesling, S., Dei Tos, A. P., Kunkler, I., Otter, R. et al. 2011. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*. 47(17), 2493–2511.
31. Government of the Netherlands. 2018. Positive outcome of joint reimbursement negotiations on Spinraza. *Government of the Netherlands*. Available from: https://www.government.nl/latest/news/2018/07/12/positive-outcome-of-joint-reimbursement-negotiations-on-spinraza [viewed 18.07.2018.].
32. Griggs, R. C., Batshaw, M., Dunkle, M., Gopal-Srivastava, R., Kaye, E., Krischer, J., Nguyen, T. et al. 2009. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab*. 96(1), 20–26.
33. Hee, S. W., Willis, A., Tudur Smith, C., Day, S., Miller, F., Madan, J., Posch, M. et al. 2017. Does the low prevalence affect the sample size of interventional clinical trials of rare diseases? An analysis of data from the aggregate analysis of clinicaltrials.gov. *Orphanet J Rare Dis*. 12:44.
34. Hutchings, A., Schey, C., Dutton, R., Achana, F. and Antonov, K. 2014. Estimating the budget impact of orphan drugs in Sweden and France 2013–2020. *Orphanet J Rare Dis*. 9:22.
35. Iskrov, G. and Stefanov, R. 2014. 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. *Centre for Analyses and Health Technology Assessment, Institute for Rare Diseases*. Available from: http://raredis.org/pub/OD_Report_2014_EN.pdf [viewed 08.07.2016.].
36. Iskrov, G., Miteva-Katrandzhieva, T. and Stefanov, R. 2012. Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria. *Health Policy*. 108, 10–18.
37. Joppi, R., Bertele, V. and Garattini, S. 2009. Orphan drug development is not taking off. *Br J Clin Pharmacol*. 67(5), 494–502.
38. Joppi, R., Bertele, V. and Garattini, S. 2013. Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU. *Eur J Clin Pharmacol*. 69(4), 1009–1024.
39. Kakkis, E. D., O'Donovan, M., Cox, G., Hayes, M., Goodsaid, F., Tandon, P. K., Furlong, P. et al. 2015. Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. *Orphanet J Rare Dis*. 10:16.
40. Kanters, T. A., de Sonneville-Koedoot, C., Redekop, W. K. and Hakkaart, L. 2013. Systematic review of available evidence on 11 high-priced inpatient orphan drugs. *Orphanet J Rare Dis*. 8:124.
41. Kanters, T. A., Steenhoek, A. and Hakkaart, L. 2014. Orphan drugs expenditure in the Netherlands in the period 2006–2012. *Orphanet J Rare Dis*. 9:154.
42. Kesselheim, A. S., Myers, J. A. and Avorn, J. 2011. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA*. 305(22), 2320–2326.
43. Kesselman, I., Elstein, D., Israeli, A.,Chertkoff, R. and Zimran, A. 2006. National health budgets for expensive orphan drugs: Gaucher disease in Israel as a model. *Blood Cells Mol Dis*. 37(1), 46–49.

44. Latvijas Biomedicīnas pētījumu un studiju centrs (BMC). 2014. Valsts iedzīvotāju genoma datu bāze. *BMC*. Iegūts no: http://biomed.lu.lv/gene/KASirgenomadatubaze.htm [sk. 29.01.2014.].
45. Le Cam, Y. 2010. Inventory of access and prices of orphan drugs across Europe: a collaborative work between national alliances on rare diseases and Eurordis. *Eurordis*. Available from: img2.eurordis.org/newsletter/pdf/mar-2011/ERTC_13122010_YLeCam_Final.pdf [viewed 02.05.2014.].
46. Logviss, K., Krievins, D. and Purvina, S. 2014. Rare diseases and orphan drugs: Latvian story. *Orphanet J Rare Dis*. 9:147.
47. Logviss, K., Krievins, D. and Purvina, S. 2016. Impact of orphan drugs on Latvian budget. *Orphanet J Rare Dis*. 11:59.
48. Maeda, H. and Kurokawa, T. 2015. Acceptance of surrogate end points in clinical trials supporting approval of drugs for cancer treatment by the Japanese regulatory agency. *Ann Oncol*. 26(1), 211–216.
49. Mechler, K., Mountford, W. K., Hoffmann, G. F. and Ries, M. 2015. Pressure for drug development in lysosomal storage disorders – a quantitative analysis thirty years beyond the US orphan drug act. *Orphanet J Rare Dis*. 10:46.
50. Meekings, K. N., Williams, C. S. and Arrowsmith, J. E. 2012. Orphan drug development: an economically viable strategy for biopharma R&D. *Drug Discov Today*. 17(13–14), 660–664.
51. Michel, M. and Toumi, M. 2012. Access to orphan drugs in Europe: current and future issues. *Expert Rev Pharmacoecon Outcomes Res*. 12(1), 23–29.
52. Ministru Kabinets. 2006. Ambulatorajai ārstēšanai paredzēto zāļu un medicīnisko ierīču iegādes izdevumu kompensācijas kārtība: MK noteikumi Nr. 899. *Latvijas Vēstnesis*. 180(3548).
53. Ministru Kabinets. 2009. Par Onkoloģisko slimību kontroles programmu 2009.–2015.gadam: MK rīkojums Nr. 48. *Latvijas Vēstnesis*. 29(4015).
54. Ministru Kabinets. 2013. Sirds un asinsvadu veselības uzlabošanas rīcības plāns 2013.–2015.gadam: MK rīkojums Nr. 359. *Latvijas Vēstnesis*. 151(4957).
55. Ministru Kabinets. 2017. Par Plānu reto slimību jomā 2017.–2020. gadam: MK rīkojums Nr. 602. *Latvijas Vēstnesis*. 212(6039).
56. Mitsumoto, J., Dorsey, E. R., Beck, C. A., Kieburtz, K. and Griggs, R. C. 2009. Pivotal studies of orphan drugs approved for neurological diseases. *Ann Neurol*. 66(2), 184–190.
57. Onakpoya, I. J., Spencer, E. A., Thompson, M. J. and Heneghan, C. J. 2015. Effectiveness, safety and costs of orphan drugs: an evidence-based review. *BMJ Open*. 5:e007199.
58. Orfali, M., Feldman, L., Bhattacharjee, V., Harkins, P., Kadam, S., Lo, C., Ravi, M. et al. 2012. Raising orphans: how clinical development programs of drugs for rare and common diseases are different. *Clin Pharmacol Ther*. 92(2), 262–264.
59. Orofino, J., Soto, J., Casado, M. A. and Oyagüez, I. 2010. Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007. *Appl Health Econ Health Policy*. 8(5), 301–315.
60. Orphanet. 2014. Rare Disease Registries in Europe. *Orphanet Report Series*. Available from: http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf [viewed 29.01.2014.].

61. Pavlović, N., Stanimirov, B., Stojančević, M., Paut-Kusturica, M., Stoimenova, A., Goločorbin-Kon, S. and Mikov, M. 2012. An insight on differences in availability and reimbursement of orphan medicines among Serbia, Bulgaria and Sweden. *Biotechnol Biotec Eq*. 26(5), 3236–3241.
62. Picavet, E., Annemans, L., Cleemput, I., Cassiman, D. and Simoens, S. 2012. Market uptake of orphan drugs – a European analysis. *J Clin Pharm Ther*. 37(6), 664–667.
63. Picavet, E., Cassiman, D., Hollak, C. E., Maertens, J. A. and Simoens, S. 2013. Clinical evidence for orphan medicinal products – a cause for concern? *Orphanet J Rare Dis*. 8:164.
64. Picavet, E., Dooms, M., Cassiman, D. and Simoens, S. 2011. Drugs for rare diseases: influence of orphan designation status on price. *Appl Health Econ Health Policy*. 9(4), 275–279.
65. Public Population Project in Genomics and Society (P3G). 2013. Genome Database of Latvian Population. *P3G*. Available from: http://www.p3gobservatory.org/catalogue.htm;jsessionid=ACE6E593F10B80573D64E965FA2DB3D8?measureId=18 [viewed 29.01.2014.].
66. Regulation (EC) No 141/2000 of the European Parliament and of the Council (16.12.1999.) on orphan medicinal products. 2000. *Off J Eur Communities*. L18, 1–5.
67. Regulation (EU) No 536/2014 of the European Parliament and of the Council (16.04.2014.) on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 2014. *Off J Eur Union*. L158, 11–53.
68. Richey, E. A., Lyons, E. A., Nebeker, J. R., Shankaran, V., McKoy, J. M., Luu, T. H., Nonzee, N. et al. 2009. Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? *J Clin Oncol*. 27(26), 4398–4405.
69. Rodwell, C. and Aymé, S. 2014. 2014 Report on the state of the art of rare disease activities in Europe. *EUCERD*. Available from: http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesV.pdf [viewed 08.08.2014.].
70. Schey, C., Milanova, T. and Hutchings, A. 2011. Estimating the budget impact of orphan medicines in Europe: 2010–2020. *Orphanet J Rare Dis*. 6:62.
71. Schlander, M., Adarkwah, C. C. and Gandjour, A. 2015. Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Rev Pharmacoecon Outcomes Res*. 15(1), 171–179.
72. Simoens, S. 2011. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis*. 6:42.
73. Slimību profilakses un kontroles centrs (SPKC). 2012a. Latvijas veselības aprūpes statistikas gadagrāmata: Mātes un bērna veselības aprūpe. *SPKC*. Iegūts no: http://www.spkc.gov.lv/veselibas-aprupesstatistika/ [sk. 18.04.2014.].
74. Slimību profilakses un kontroles centrs (SPKC). 2012b. Statistikas dati par bērnu veselību Latvijā. *SPKC*. Iegūts no: http://www.spkc.gov.lv/veselibas-aprupes-statistika/ [sk. 18.04.2014.].
75. Slimību profilakses un kontroles centrs (SPKC). 2013. Onkoloģija: Statistikas dati par pacientu skaitu sadalījumā pa reģioniem, lokalizācijas veidiem, dzimuma un vecuma grupām no 2009. gada līdz 2012. gadam. *SPKC*. Iegūts no: http://www.spkc.gov.lv/veselibas-aprupes-statistika/ [sk. 18.04.2014.].

76. Spokiene, I. 2008. Legal assessment of current situation on orphan patients in Lithuania. *Medicina (Kaunas)*. 44(8), 571–576.
77. Unkel, S., Röver, C., Stallard, N., Benda, N., Posch, M., Zohar, S. and Friede, T. 2016. Systematic reviews in paediatric multiple sclerosis and Creutzfeldt-Jakob disease exemplify shortcomings in methods used to evaluate therapies in rare conditions. *Orphanet J Rare Dis*. 11:16.
78. Valsts informācijas sistēmu reģistrs. 2012. Ar noteiktām slimībām slimojošu pacientu reģistrs. *Valsts informācijas sistēmu reģistrs*. Iegūts no: https://www.visr.eps.gov.lv/visr/default.aspx?action=2&rid=138 [sk. 29.01.2014.].
79. Veselības ekonomikas centrs. 2009. Par Novartis Pharma Services Inc. pārstāvniecības Latvijā iesniegumiem par medikamentu Glivec apvalkotās tabletes 400 mg Nr. 30 un Glivec apvalkotās tabletes 100 mg Nr. 120 iekļaušanu Kompensējamo zāļu sarakstā un Imatinibum pacientu skaitu 2010. gadā: Veselības ekonomikas centra (22.12.2009.) lēmums Nr. 995. *Latvijas Vēstnesis*. 15(4207).
80. Veselības ekonomikas centrs. 2010. Par Novartis Pharma Services Inc. pārstāvniecības Latvijā medikamentu Glivec cietās kapsulas 100 mg Nr. 120, Glivec apvalkotās tabletes 400 mg Nr. 30 un Glivec apvalkotās tabletes 100 mg Nr. 120 pacientu skaitu zāļu iegādes kompensācijas sistēmā: Veselības ekonomikas centra (21.12.2010.) lēmums Nr. 686. *Latvijas Vēstnesis*. 16(4414).
81. Veselības ministrija. 2013. Plāns reto slimību jomā 2013.–2015. gadam: Veselības ministrijas (20.06.2013.) rīkojums Nr. 110. *Veselības ministrija*. Iegūts no: http://www.vm.gov.lv/images/userfiles/reto_slimibu_plans_13_15.pdf [sk. 29.01.2014.].
82. Winstone, J., Chadda, S., Ralston, S. and Sajosi, P. 2015. Review and comparison of clinical evidence submitted to support European Medicines Agency market authorization of orphan-designated oncological treatments. *Orphanet J Rare Dis*. 10:139.
83. World Bank. 2016a. Data on GDP per capita (PPP). *World Bank*. Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD [viewed 02.03.2016.].
84. World Bank. 2016b. Data on total population. *World Bank*. Available from: http://data.worldbank.org/indicator/SP.POP.TOTL [viewed 02.03.2016.].
85. Ylä-Herttuala, S. 2015. Glybera's second act: the curtain rises on the high cost of therapy. *Mol Ther*. 23(2), 217–218.

PUBLICATIONS AND THESES ON RESEARCH TOPIC

PUBLICATIONS

Publications in international peer-reviewed scientific journals:

1) Logviss, K., Krievins, D. and Purvina, S. 2014. Rare diseases and orphan drugs: Latvian story. *Orphanet J Rare Dis*. 9:147.
2) Logviss, K., Krievins, D. and Purvina, S. 2016. Impact of orphan drugs on Latvian budget. *Orphanet J Rare Dis*. 11:59.
3) Logviss, K., Krievins, D. and Purvina, S. 2018. Characteristics of clinical trials in rare vs. common diseases: A register-based Latvian study. *PLoS One*. 13(4):e0194494.
4) Logviss, K., Krievins, D. and Purvina, S. 2013. Orphan Drugs in Surgery. *Acta Chirurgica Latviensis*. 13(1), 57–62.
5) Logviss, K., Krievins, D. and Purvina, S. 2014. Trends in individual reimbursement of orphan drugs in Latvia in 2008–2011. Proceedings of the 4th International Interdisciplinary Scientific Conference „Society, Health, Welfare". *SHS Web of Conferences.* 10:00021.

Publications in Latvian peer-reviewed scientific journal:

Logviss, K., Krieviņš, D. un Purviņa, S. 2011. Retās slimības un orfānzāles Latvijā. *RSU Zinātniskie raksti*. 1, 313–317.

THESES (ABSTRACTS, POSTERS AND ORAL REPORTS)

International scientific conferences:

1) Logviss, K., Krievins, D. and Purvina, S. 2012. Trends in reimbursement of orphan drugs in Latvia within the framework of individual reimbursement system in 2008–2010. *International Conference in Pharmacology „Targeting Cellular Regulatory Systems"*. Riga, Latvia, 20–21.04.2012. Poster and thesis.
2) Logviss, K., Krievins, D. and Purvina, S. 2012. Trends in reimbursement of orphan drugs in Latvia within the framework of individual reimbursement system in 2008–2011. *4th International Interdisciplinary Scientific Conference „Society, Health, Welfare"*. Riga, Latvia, 22–23.11.2012. Poster and thesis.
3) Logviss, K., Krievins, D. and Purvina, S. 2011. Rare diseases in Latvia, current diagnostic and treatment options. *2nd South Caucasian Conference on Rare Diseases and Orphan Drugs*. Tbilisi, Georgia, 27–28.10.2011. Thesis.
4) Logviss, K., Bitina, S., Krievins, D. and Purvina, S. 2011. Rare diseases in Latvia, current diagnostic and treatment options. *6th Baltic Sea Region Conference in Medical Sciences*. Riga, Latvia, 29.04–01.05.2011. Poster.

International conference (congress):

Logviss, K., Krievins, D. and Purvina, S. 2011. Rare diseases in Latvia, current diagnostic and treatment options. *BaltPharm Forum*. Ventspils, Latvia, 28.05.2011. Poster.

Local scientific conferences:

1) Logviss, K., Krieviņš, D. un Purviņa, S. 2011. Retās slimības un orfānmedikamenti Latvijā. *RSU 10. zinātniskā konference*. Riga, Latvia, 14–15.04.2011. Oral report and thesis.
2) Logviss, K., Krieviņš, D. un Purviņa, S. 2012. Reto slimību ārstēšanai domāto zāļu kompensēšanas tendeces Latvijā individuālās kompensācijas ietvaros 2008.–2010. gadā. *RSU 11. zinātniskā konference*. Riga, Latvia, 29–30.03.2012. Poster and thesis.
3) Logviss, K., Krievins, D. and Purvina, S. 2013. Clinical trials of orphan drugs in Latvia. *RSU 12. zinātniskā konference*. Riga, Latvia, 21–22.03.2013. Poster and thesis.