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ORIGINAL ARTICLE

Orphan Drugs in Surgery

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Summary
Introduction. Rare diseases, also called orphan diseases, are life-threatening or chronically debilitating conditions of different origin. Majority of them are genetic disorders, others being rare cancers, congenital malformations, autoimmune, toxic and infectious diseases. Rare conditions may also be related to surgery, e.g. acute sensorineural hearing loss after surgery induced acoustic trauma, scarring post glaucoma filtration surgery, and short bowel syndrome following intestinal surgery. Besides, surgery as a specific area for orphan drugs, has not been studied yet in Latvia.
Aim of the study. This study aims to determine orphan drugs associated with surgery (used pre-, during or post-surgery) and their availability and access in Latvia.
Materials and methods. European register of designated orphan medicinal products and EMA approved Summary of Product Characteristics were analyzed, to find orphan drugs with approved labeled indications related to surgery. Drug availability and access in Latvia were determined, by using data available from State Agency of Medicines of Latvia and National Health Service. A literature review was performed to compare Latvian situation in field of orphan medicines with other European countries.
Results. 15 orphan drugs were identified, 8 of them (53.3%) indicated for different kinds of tumors. 6 drugs (40%) are available in Latvia, including one drug (6.7%) included in the reimbursement list.
Conclusions. Oncology is the biggest therapeutic area of orphan drugs. Majority of orphan drugs are not available in Latvia, moreover those drugs that are available are often not accessible.
Key words: orphan drugs; rare diseases; surger; Latvia.

INTRODUCTION

Rare diseases, also related to as orphan diseases, are life-threatening or chronically debilitating conditions of different origin. The majority of them are genetic disorders, others being rare cancers, congenital malformations, autoimmune, toxic and infectious diseases. These rare conditions may also be related to surgery, e.g. acute sensorineural hearing loss after surgery induced acoustic trauma, scarring post glaucoma filtration surgery, and short bowel syndrome following intestinal surgery. Relatively often these conditions are associated with transplantation, for example: ischemia/reperfusion injury associated with solid organ transplantation and recurrent hepatitis C virus induced liver disease in liver transplant recipients. (20) Disease is considered as rare if it affects not more than 1 in 2 000 people in the European Union (EU). It is estimated that between 5 000 and 8 000 different rare conditions exist, affecting 6-8% of the population, concluding that about 30 million people are suffering from rare diseases in the EU. (4)

The EU offers a range of incentives to foster the development of orphan drugs since, under normal market conditions, pharmaceutical companies have little interest in developing drugs intended for small numbers of patients. These incentives include assistance with medicine development, reduced fees for marketing authorization, protection from market competition once the medicine is authorized (10 years of marketing exclusivity). (21) Orphan designation refers to awarding of orphan status to a medicine, but marketing authorization refers to the approval to market the medicine. While many drugs may have received an orphan designation, few have received a marketing authorization. As of March 2013 there are 921 positive opinions on orphan designation and 65 orphan drugs authorized in the EU. Four drugs were withdrawn from use in the EU and six drugs have already completed their period of market exclusivity. (13, 20)

There is a limited public awareness of the rare diseases in general. The national healthcare services for rare diseases differ significantly among the EU Member States, resulting in unequal access to diagnostics and treatment (including orphan drugs). Considering this European Council recommended Member States to establish and implement national plans for rare diseases by the end of 2013. (5) Currently there is no approved national plan for rare diseases in Latvia. A working group for the plan development was established in Ministry of Health in 2010. The plan project called "National Plan for Rare Diseases in Latvia in 2012-2015" was developed by the group and submitted for further public discussion. (15)

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. Drug reimbursement covers drugs which are included in the Latvian 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 limit of 10 000 LVL (€14 229) per patient per year. (15) The main principle of drug inclusion in the reimbursement list is that drug should be therapeutically and cost effective, i.e. decision is value based and is not specific to orphan drugs. The national reimbursement list consists of 3 parts: list A covering therapeutically equivalent drugs; list B that consists of drugs without therapeutic equivalent; and list C that contains drugs for which the annual cost exceeds 3 000 LVL (€4 269) 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 National Health Service 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 other EU countries. The price of 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 medicine in Estonia and Lithuania. (16)

Currently 29 orphan drugs are available on Latvian market, including 4 drugs that were originally designated orphan medicines, but further withdrawn from the EU register of designated orphan medicinal products upon request of the sponsor (eltrombopag, everolimus, imatinib, and sunitinib). (9) Three drugs are included in the reimbursement list C (imatinib, dasatinib, and nilotinib) all indicated for Philadelphia chromosome positive chronic myeloid leukemia. (22) 13 drugs were reimbursed within the framework of individual reimbursement system in 2008-2012, and four drugs (betaine, idursulfase, mecasermin, and sapropterin) were provided within the program of medicinal treatment of rare diseases in children. Orphan drugs are distributed by both hospital and community pharmacies in Latvia.

All drugs must be authorized before they can be marketed in the EU. However, a first level of accessibility exists for orphan drugs that have not yet been authorized, the most common being compassionate use. It covers diseases for which no satisfactory alternative therapy exists. State Agency of Medicines has approved several programs for drug compassionate use in Latvian hospitals. The programs include influenza medicines (oseltamivir and zanamivir) for intravenous administration, medicine for chronic hepatitis C (boceprevir), and drugs for cancer (dasatinib and pazopanib) used in chronic Philadelphia positive leukemia and metastatic soft tissue sarcoma. Dasatinib (Sprycel) is an orphan drug included in the national reimbursement list C, while pazopanib (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. (3)

AIM OF THE STUDY

This study aims to determine orphan drugs associated with surgery (used pre-, during or post-surgery) and their availability and access in Latvia.

MATERIAL AND METHODS

European register of designated orphan medicinal products (http://ec.europa.eu/health) was used to identify orphan drugs in Europe with European orphan designation and European marketing authorization. For all authorized orphan drugs Summary of Product Characteristics (SPC) approved by European Medicines Agency (http://www.ema.europa.eu) were analyzed to find drugs with approved labeled indications related to surgery (used pre-, during or post-surgery). These indications are not necessarily orphan designated indications of orphan drugs with multiple labeled indications.

For orphan drugs that fulfilled inclusion criteria availability on Latvian market was determined by using National Register of Human Medicines maintained by State Agency of Medicines of Latvia (http://www.zva.gov.lv), as well as directly contacting drug manufacturers and wholesalers. The National Health Service (http://www.vmnvd.gov.lv) data were used to assess drug reimbursement including national reimbursement list and individual reimbursement data in 2008-2012. A literature review was performed to compare Latvian situation in field of orphan medicines with other European countries.

RESULTS

A total of 15 orphan drugs were identified that are used pre-, during or post-surgery (Table 1). 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.

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 European Medicines Agency 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 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 (FAP), 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 re-opens, 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 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 and the hypereosinophilic syndrome, and myelodysplastic/ myeloproliferative diseases.

6 out of 15 orphan drugs (40%) included in the analysis are available on Latvian market (Table 2). 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, is included in the reimbursement list C. Drugs included in the list are reimbursed for a particular indication, but not for all labeled indications. For imatinib the reimbursed conditions are chronic myeloid leukemia and bone marrow transplantation. All other drugs can 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. The Marketing Authorization Holder (MAH) is obligated to implement mentioned training course. According to information provided by MAH there is one neurosurgeon in Latvia experienced in utilizing the product.

The National Health Service 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 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 Children Clinical University Hospital may be mentioned, as it manages a program of medicinal treatment of rare diseases in children and additional budget resources are available for this program.

DISCUSSION

Our study indicates that majority of orphan drugs associated with surgery are used in oncology field. As well 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, since survey conducted by the European Organization for Rare Diseases (Eurordis) in 2010 found that rare oncological conditions represented 38% of authorized orphan medicines and 56% of patients potentially treated with these medicines. (12) Similar results were reported by Schey et al. stating that within the total budget impact 40% of the conditions, for which orphan drugs were marketed, were oncological and hematological diseases, accounted for 57% of the total costs in 2010. (23) 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. Whereas historically orphan indications were focused mostly on congenital, metabolic, oncologic and hematologic diseases, now 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 future by the advanced therapies and cell therapies studied recently.

Another finding is that majority of orphan drugs included in the analysis are not available on Latvian market, and only one of studied drugs (imatinib) is included in the reimbursement list. Moreover imatinib is accessible only partially since it is reimbursed for two conditions, while it has six designated orphan indications in the EU. As stated by Drummond et al., because of the small market, orphan drugs are often very expensive. With standard economic evaluation, these drugs usually do not prove to be cost-effective and it, taking into account their high price, means that patient access may be limited. (10) According to Picavet et al. orphan designated drugs have higher median price (€138.56) than non-designated drugs (€16.55) for rare disease indications. (19) Moreover price of an orphan drug is higher for a

disease with a lower prevalence. (6) Although orphan drugs with an alternative have lower annual cost per patient than those without an alternative. (24)

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. (1) Thus in 2010, the number of patients with potential access to orphan drugs ranged from 34% in Greece up to 98% in France. The price also varied between countries, and in some countries it was up to 160% higher than the lowest European price. (12) Another European study found that differences in annual costs per patient between EU countries for a given orphan drug may reach 70%. (6) Denis et al. compared rare disease and orphan drug markets in six European countries. The situation on orphan drug reimbursement in 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). (7)

Newer EU Member States are often facing budget restrictions with healthcare budgets much lower than compared to older Member States, thereby reimbursement levels can differ. (14) Thus number of available (marketed) orphan drugs in Bulgaria was 22 and 16 of them were accessible (reimbursed) for patients in 2011. Iskrov et al. point 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. (11) Serbia might be mentioned as another example, where only four orphan medicines were reimbursed. Authors also suggest that gross domestic product (GDP) value may partly explain differences in the level of orphan drug reimbursement among European countries, since Serbia is a country with a low GDP. (18) In Lithuania budget assigned for reimbursement of orphan medicines is limited and insufficient (6.5 million LTL, i.e. €1.89 million, in 2006), therefore access to health care services and orphan drugs in some cases is restricted. (25)

Currently 29 orphan drugs are available in Latvia, and only three of them are included in the reimbursement list C (imatinib, dasatinib, and nilotinib) all indicated for Philadelphia chromosome positive chronic myeloid leukemia. Thus number of reimbursed orphan drugs in Latvia is smallest among the all European countries included in the analysis. Whereas orphan drugs can also be reimbursed individually with limit of 10 000 LVL (€14 229) per patient per year, this limit is certainly not sufficient. All the other orphan medicines, that are not reimbursed, are practically inaccessible for Latvian patients because of their high costs.

Pharmaceutical companies have to comply with different pricing and reimbursement approaches in each EU country, thereby raising the price of orphan drugs. (2) 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, there is a need for a transparent and evidence based approach towards pricing and reimbursement of orphan drugs. (24)

The economic impact of orphan drugs on national budget is growing, for example, in France representing a total budget of €1 billion in 2009. (14) The annual per patient cost of orphan drugs varied between €1 251 and €407 631, with the median cost being €32 242. The share of the total European pharmaceutical market represented by orphan drugs was 3.3% in 2010, and it was predicted by Schey et al. to increase to a peak of 4.6% in 2016. (23) Another analysis estimated that orphan drugs constituted 1.9% of total drugs expenditure in Belgium in 2008, and predicted it to increase to about 4% in 2013. (8) While the average budget impact of orphan drugs accounted for 1.7% of the total pharmaceutical expenditure across France, Germany, Italy, Spain and the UK in 2007. (17)

CONCLUSIONS

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.

Majority of orphan drugs 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.

Conflict of interest: None

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Table 1. Orphan drugs associated with surgery

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 (intraspinal use)	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 hydrochloride	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
Busulfan (intravenous use)	Busilvex	Conditioning treatment prior to conventional hematopoietic progenitor cell transplantation (HPCT)
Thiotepa	Tepadina	Conditioning treatment prior to allogeneic or autologous HPCT in hematological diseases; when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumors
Plerixafor	Mozobil	Treatment to mobilize hematopoietic stem cells for subsequent autologous transplantation in patients with lymphoma and multiple myeloma

Table 2. Surgery related orphan drugs available in Latvia

Active substance	Trade name	Reimbursement category	Reimbursement conditions
Imatinib	Glivec	List C	Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (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
5-aminolevulinic acid hydrochloride	Gliolan	Individual	These drugs are available in Latvia, but are neither included in the reimbursement list, nor reimbursed individually in 2008-2012
Ibuprofen	Pedea		