Uniwersytet Jagielloński
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Ocena polityki refundacyjnej w odniesieniu do leków sierocych w Polsce i w Europie

Praca doktorska

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Spis treści

Wstęp

Nie istnieje jedna uznana definicja choroby rzadkiej, jednak w każdym przypadku definicja bazuje na rozpowszechnieniu, które waha się of 1 do 8 przypadków na 10 000 osób. W Unii Europejskiej (UE) choroba jest uznawana przez Europejską Agencję Leków (EMA) za rzadką, gdy jest chroniczna lub zagrażająca życiu oraz jej rozpowszechnienie nie przekracza 5 przypadków na 10 000 osób, co odpowiada około 250 000 przypadków danej choroby w całej UE. Leki stosowane w terapii chorób rzadkich nazywane są lekami sierocymi (*Orphan Drugs; OD*), co spowodowane jest faktem niedostatecznej ich ilości. Większość chorób rzadkich pozostaje bez rozwiązania terapeutycznego, a niewielka ilość chorych powoduje, że choroby rzadkie często nie znajdują się 'na celowniku' przedsiębiorstw farmaceutycznych, ze względu na ograniczony rynek zbytu oraz ogromne koszty wytworzenia nowego produktu leczniczego.

W celu zachęcenia firm farmaceutycznych do wejścia na rynek leków sierocych stosowane są dodatkowe zabiegi jak np. wydłużona ochrona patentowa. W UE leki sieroce oznaczane są tzw. *Orphan Designation* oraz autoryzowane są w ramach procedury centralnej, dającej dostęp do całego runku UE; jednakże kwestia refundacji danego leku pozostaje w decyzji odpowiednich agencji krajów członkowskich. W zależności od kraju i zaimplementowanego systemu Oceny Technologii Medycznych (HTA) dodatkowe ciała doradcze mogą wydawać najczęściej niewiążące opinie lub rekomendacje dotyczące zasadności refundacji danego leku w danym wskazaniu – w niektórych krajach członkowskich leki sieroce oceniane są wg odrębnych przepisów.

Podejmowanie decyzji oraz rekomendacji refundacyjnych dotyczących leków sierocych może być utrudnione przez brak wystarczających danych klinicznych dotyczących skuteczności i profilu bezpieczeństwa oraz informacji dotyczących zarówno kosztów bezpośrednich (w tym zazwyczaj wysokiej ceny leku) jak i kosztów pośrednich.

Dodatkowym czynnikiem, który może mieć wpływ na sytuację refundacyjną danego leku jest jego status autoryzacyjny nadawany przez EMA, który może przyjąć jedną z trzech form: autoryzacja bez dodatkowych warunków, autoryzacja warunkowa (*conditional approval*) oraz autoryzacja na zasadach specjalnych (*exceptional circumstances*).

Złożoność procesu formułowania rekomendacji oraz podejmowania decyzji refundacyjnych wymaga nie tylko jakościowej analizy polegającej na przeglądzie aktów prawnych i systemów organizacji finansowania zdrowia publicznego w danych krajach, lecz również oceny ilościowej polegającej na badaniu wpływu tych czynników na rekomendacje i decyzje

refundacyjne oraz oceny zgodności rekomendacji i decyzji refundacyjnych wewnątrz i pomiędzy krajami członkowskimi UE. Ze względu na wysokie koszty leków sierocych, problem ten może szczególnie dotyczyć krajów Europy Środkowo-Wschodniej (CEE).

Celem niniejszej pracy jest kompleksowa, jakościowa oraz ilościowa analiza polityki refundacyjnej w stosunku do leków sierocych w Polsce i Europie, ze szczególnym uwzględnieniem krajów Europy Środkowo-Wschodniej oraz leków stosowanych w terapiach rzadkich schorzeń onkologicznych.

Publikacja 1:

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Refundacja leków sierocych jest ogromnym wezwaniem dla systemu opieki zdrowotnej krajów członkowskich UE nie tylko administracyjnym i prawnym ale też budżetowym. W sytuacji ograniczonych zasobów może dochodzić do selektywnej refundacji leków, która ma doprowadzić to maksymalizacji efektu zdrowotnego dla całej populacji, co może doprowadzać do znacznych różnic w odsetku refundowanych leków posiadających *orphan designation* pomiędzy krajami członkowskimi UE oraz do różnic we wpłynie czynników związanych z rejestracją na status refundacyjny danego leku.

Celem tego opracowania była analiza odsetka refundowanych leków sierocych w Belgii, Danii, Anglii, Francji, Niemczech, Włoszech, Polsce, Szkocji, Hiszpanii, Szwecji, Holandii oraz Walii oraz ocena zgodności decyzji refundacyjnych pomiędzy tymi krajami w odniesieniu do w/w leków. Dodatkowo ocenie będzie podlegał wpływ rodzaju autoryzacji nadawanej przez EMA, typu choroby, w której terapii ma być dany lek sierocy stosowany oraz ich interakcja na decyzję refundacyjną.

Badanie pokazało, że odsetek refundowanych leków sierocych waha się znacznie pomiędzy krajami od 27% w Polsce do 88% w Danii; podobnie znaczną zmienność zaobserwowano w przypadku zgodności w decyzjach refundacyjnych, z których największa wystąpiła pomiędzy Włochami i Hiszpanią (κ=0.64), a najmniejsza pomiędzy Anglią i Niemcami (κ=0.01). Spostrzeżono również istotny wpływ rodzaju autoryzacji na decyzję refundacyjną w niektórych z analizowanych krajów.

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Reimbursement of Orphan Drugs in Europe in Relation to the Type of Authorization by the European Medicines Agency and the Decision Making Based on Health Technology Assessment

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Objective: To assess shares of reimbursed orphan drugs and agreement in reimbursement decision-making in different European Union member states as well as to define odds for reimbursement influenced by the presence of conditional approval or exceptional circumstances granted by the European Medicines Agency (EMA) or by type of the disease.

Methods: The list of authorized drugs with current orphan designations was collected from the website of the EMA. For each drug, the information regarding conditional approval or approval under exceptional circumstances was collected. The reimbursement statuses were available on national reimbursement or HTA agencies websites. The agreement for reimbursement decisions between selected countries was assessed using the κ coefficient for the measurement of agreement. The impact of the EMA's conditional approval as well as approval under exceptional circumstances was assessed using the logistic regression and presented as odds ratio.

Results: The percentage of reimbursed orphan drugs varied significantly from 27% in Poland to 88% in Denmark, with an average value of 51% ($p < 0.0001$). Regarding the reimbursement status, the highest, substantial agreement was observed between Spain and Italy, and the lowest agreement was observed between Germany and England, with κ of 0.64 and 0.01, respectively. Conditional approval status significantly decreased the chance for reimbursement in France, Italy, and Spain by 77–80%; however, approval granted under exceptional circumstances had significant impact only in Germany with 85% decrease in chances for reimbursement. The type of the disease (oncology or metabolic) was significantly associated with both conditional approval (p of 0.03—oncology drugs were more likely to be conditionally approved then the rest of analyzed drugs) and exceptional circumstances (p of 0.02—drugs for metabolic diseases were more likely to be approved under exceptional circumstances).

Conclusions: Access to reimbursed orphan drugs varies significantly across EU countries. The highest, substantial agreement in reimbursement decisions was observed between Italy and Spain and the lowest between Germany and England. Conditional approval and approval under exceptional circumstances were significant negative predictors of reimbursement in some countries and they were significantly associated with the type of the disease (oncology or metabolic).

Keywords: EMA (European Medicines Agency), orphan drugs for rare diseases, reimbursement, authorization, HTA (Health Technology Assessment)

BACKGROUND

There is no common definition of an orphan drug, which is the reason for discrepancies among the definitions implemented by different countries in their drug reimbursement decision-making process. However, there is general acceptance that the definition should be based on the prevalence of rare diseases treated by orphan drugs. According to the current definition provided by the European Union (EU), rare diseases mostly include inherited, life-threatening, or chronically debilitating diseases that affect fewer than 5 out of 10,000 people (EMEA, 2017). The assumed threshold prevalence varied from 1 to 8 per 10,000 people (Winstone et al., 2015). According to the definition by the European Medicines Agency's (EMA), the prevalence is 5 persons per 10,000, which translates into around 246,000 people affected by rare diseases, considering 27 EU member states (Winstone et al., 2015; EMEA, 2017).

Different types of rare diseases can be defined and the broadest categories include oncologic diseases (around 32.5% of all orphan drugs; Gammie et al., 2015) and metabolic conditions. As orphan diseases have mostly genetic origin both oncologic and metabolic orphan drugs are of special interest for EMA.

In order for a drug to fulfill the EMA's conditions of orphan drugs, it needs to be used for the diagnosis, prevention, or treatment of patients with a life-threatening or chronically debilitating condition. The EMA's definition includes also drugs that are unlikely to generate sufficient profit to justify research and development costs (Winstone et al., 2015; EMEA, 2017). This doubtful and uncertain return on the investment makes the health technology assessment (HTA) process very difficult and challenging because the required data on clinical efficacy and safety as well as data pertaining to costs may simply be insufficient. What makes the reimbursement decision even harder is the fact that orphan drugs are generally more expensive than non-orphan drugs due to frequent genetic etiology of the targeted disease (EMEA, 2017), which translates into significant budget impact despite a low number of potential patients. It is an important aspect of proper allocation of public finances presenting a major problem for public health and decision-making. This fact may be reflected in substantial variation of reimbursement decisions for orphan drugs among EU state members.

Orphanet (https://www.orpha.net/consor/cgi-bin/index.php) is a reference portal with information on rare diseases and orphan drugs for all audiences. Its goal is to gather and improve knowledge on rare diseases, their diagnosis, and nomenclature as well as care and treatment of patients with these diseases (Orphanet, 2018).

To help national decision-makers as well as national HTA agencies, the EMA issues a conditional marketing authorization (also known as a conditional approval) indicating that the medicine is addressed to fulfill important and unmet treatment needs of patients (which is often the case in patients with rare diseases). The data for the approval are less comprehensive than normally required. The presented data, however, are demanded to indicate that potential benefits from applying the treatment are higher than potential losses (risks). The marketing authorization holder is then obligated to provide a comprehensive body of clinical evidence in the future, usually within a time frame negotiated with the EMA. This conditional approval could be a signal for national decision-makers that comprehensive data will be available (EMA, 2017).

However, in some cases the condition to be treated is rare or the collection of detailed information is impossible or unethical. In these situations, the EMA may grant a marketing authorization in absence of comprehensive data under exceptional circumstances. It is a type of marketing authorization granted to medicines of which the marketing authorization holder is unable (and will probably never be able) to provide comprehensive data on the efficacy and safety under normal conditions of use.

Unlike conditional marketing authorization, in which marketing approval is granted in the likelihood that the sponsor will provide such data within an agreed time frame, authorization under exceptional circumstances can be granted when comprehensive data cannot be obtained even after authorization. This could be an important signal for national decision-makers and could potentially influence their decision, especially in a situation of a very limited budget (Commission Regulation, 2006).

Our objective was to assess the share of reimbursed orphan drugs as well as the agreement in reimbursement decision-making in different EU member states; we would like to evaluate if reimbursement decisions are influenced by the presence of conditional approval or exceptional circumstances granted by EMA. In addition the impact of type of disease (oncologic or metabolic) on conditional approval and approval under exceptional circumstances was examined.

METHODS

The list of authorized drugs with current orphan designations was collected from the EMA website (on 24 January 2017) (EMA, 2018). A list of countries that had databases of reimbursed drugs publicly available and that allowed for such an analysis to be performed was composed. The reimbursement status of each drug was collected for Belgium, Denmark, England, France, Germany, Italy, Poland, Scotland, Spain, Sweden, The Netherlands, and Wales (**Tables 1**, **2**). To perform sophisticated and in-depth analysis, data on recommendations were also collected for selected countries. The links to national websites

TABLE 1 | Review of pricing strategies and reimbursement decision making process for orphan drugs in different European countries (Panteli et al., 2016).

Country	Pricing	Managed entry agreements	Reimbursement requirements and decision-making—other remarks
Belgium	• External reference pricing • Internal reference pricing • Value-based pricing • Negotiations	Financial arrangement	Belgium is a member of BeNeLuxA initiative (BeNeLuxA Initiative, 2018). For orphan drugs a budget impact analysis is required in the reimbursement dossier but a cost-effectiveness analysis is not. In addition, the reimbursement dossiers are not publicly available (Denis et al., 2011)(Picavet et al., 2014).
Denmark	• Internal reference pricing • Competition (retail) • Tendering (hospitals)	Financial arrangement Linked to optimizing Utilization	Reimbursement decisions are based on therapeutic effect, value added, and safety profile. In addition, the price comparisons and economic analyzes are also required in the decision-making process. The Danish Medicines Agency (a board that runs parallel to National Board of Health under the Danish Ministry of Health) decides on the reimbursement status of each drug. In addition, the Reimbursement Committee makes the recommendations and advises Danish Medicines Agency before they make any decision on whether or not to reimburse a particular drug (Møller Pedersen, 2003; Olejaz et al., 2012).
England, Scotland, Wales	• Value-based pricing • Negotiations • Profit margins	Financial arrangement, financial arrangement Linked to optimizing Utilization and primarily evidence Generation	The Rare Diseases Advisory Group exists in NHS England, NHS Scotland, NHS Wales, and NHS Northern Ireland in order to make recommendations developing and implementing the strategy for rare diseases and highly specialized services (RDAG, 2018).
France	• External reference pricing • Internal reference pricing • Value-based pricing • Negotiations	Financial arrangement	Orphan drugs undergo the same HTA, pricing, and reimbursement procedures as the other drugs (Young et al., 2017).
Germany	• External reference pricing • Internal reference pricing • Value-based pricing	Financial arrangement and financial arrangement Linked to optimizing Utilization	Orphan drugs undergo the same, pricing and reimbursement procedures as the other drugs. Benefits of particular treatments are considered proven when the drug is authorized (Young et al., 2017).
Italy	• External reference pricing • Internal reference pricing • Value-based pricing • Negotiations	Financial arrangement and financial arrangement Linked to optimizing Utilization	Orphan drugs undergo the same HTA and reimbursement procedures as the other drugs. The pricing of orphan drugs benefits from more relaxed regulations and accepted levels of uncertainty (Young et al., 2017).
Poland	• External reference pricing • Internal reference pricing • Value-based pricing • Negotiations	Financial arrangement	Orphan drugs undergo the same HTA, pricing, and reimbursement procedures as the other drugs (Tordrup et al., 2014).
Spain	• External reference pricing • Internal reference pricing	Financial arrangement and financial arrangement Linked to optimizing Utilization	Orphan drugs undergo the same HTA, pricing, and reimbursement procedures as the other drugs (Young et al., 2017).
Sweden	• Internal reference pricing • Value-based pricing • Tendering	Financial arrangement and financial arrangement Linked to optimizing Utilization	Orphan drugs undergo the same pricing and reimbursement procedures as the other drugs. The HTA process can accept more relaxed assumptions (Young et al., 2017).
The Netherlands	• External reference pricing • Internal reference pricing • Negotiations	Primarily evidence Generation	Negotiations are confidential and applied only to orphan drugs (Panteli et al., 2016).

HTA, health technology assessment; NHS, National Health Service.

TABLE 2 | Reimbursement status of analyzed orphan drugs in selected countries.

Medicine name	Belgium	Denmark	England	France	Germany	Italy	Poland	Scotland	Spain	Sweden	The netherlands	Wales
Adcetris	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✓
Adempas	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alprolix	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✓	✗
Arzerra	✗	✓	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗
Atriance	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗	✓
Blincyto	✗	✓	✗	✗	✓	✗	✗	✓	✗	✗	✗	✓
Bosulif	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bronchitol	✗	✓	✓	✗	✓	✗	✗	✓	✗	✗	✗	✗
Carbaglu	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗
Cayston	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✓
Ceplene	✗	✓	✗	✓	✓	✗	✗	✗	✗	✓	✗	✗
Cerdelga	✓	✓	✓	✓	✓	✗	✗	✗	✓	✗	✗	✗
Coagadex	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Cometriq	✗	✓	✓	✗	✓	✗	✗	✗	✗	✓	✓	✓
Cresemba	✗	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓
Cystadane	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗
Dacogen	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✓	✗
Darzalex	✓	✓	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗
Defitelio	✗	✓	✓	✗	✗	✗	✗	✓	✗	✗	✓	✓
Deltyba	✗	✗	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗
Diacomit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Elaprase	✓	✓	✓	✗	✓	✓	✓	✗	✓	✗	✗	✗
Esbriet	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Farydak	✓	✓	✓	✗	✓	✗	✗	✓	✗	✗	✓	✗
Firazyr	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓
Firdapse[a]	✗	✓	✓	✓	✓	✗	✗	✓	✗	✗	✓	✗
Galafold	✓	✓	✓	✓	✓	✗	✗	✓	✗	✓	✗	✓
Gazyvaro	✓	✓	✓	✗	✓	✗	✓	✓	✓	✗	✓	✗
Gliolan	✓	✓	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗
Glybera	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Granupas[b]	✗	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗
Hetlioz	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗
Holoclar	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗
Iclusig	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Idelvion	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗
Imbruvica	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imnovid[c]	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓
Increlex	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inovelon	✓	✓	✗	✓	✓	✓	✗	✓	✓	✓	✓	✓
Kalydeco	✓	✓	✓	✓	✗	✓	✗	✗	✓	✗	✓	✓
Kanuma	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Ketoconazole HRA	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✗	✗
Kolbam	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Kuvan	✓	✓	✓	✓	✓	✓	✗	✗	✓	✗	✓	✗
Kyprolis	✓	✓	✗	✗	✓	✓	✗	✗	✓	✗	✗	✗
Lartruvo	✗	✓	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗
Lenvima	✗	✓	✗	✓	✓	✓	✗	✓	✓	✗	✓	✗
Lynparza	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✗
Mepact	✗	✓	✗	✓	✓	✓	✗	✓	✓	✗	✗	✗
Mozobil	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓
Nexavar	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓

(Continued)

TABLE 2 | Continued

Medicine name	Belgium	Denmark	England	France	Germany	Italy	Poland	Scotland	Spain	Sweden	The netherlands	Wales
NexoBrid	✓	✓	✗	✗	✓	✓	✗	✗	✗	✗	✗	✗
Ninlaro	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗
Nplate	✓	✓	✗	✓	✓	✓	✗	✓	✓	✗	✓	✗
Ocaliva	✗	✓	✓	✓	✓	✗	✗	✓	✗	✗	✗	✗
Ofev	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✗
Onivyde	✗	✓	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗
Opsumit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Orphacol	✗	✓	✓	✓	✓	✗	✗	✗	✓	✗	✓	✗
Peyona[d]	✗	✓	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗
Plenadren	✗	✓	✗	✗	✓	✓	✗	✓	✗	✗	✗	✗
Procysbi	✗	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗
Ravicti	✗	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗
Raxone	✗	✓	✓	✗	✓	✗	✗	✓	✗	✓	✓	✗
Revestive	✗	✓	✓	✓	✓	✗	✗	✗	✓	✗	✗	✗
Revlimid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Scenesse	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Signifor	✗	✓	✗	✓	✓	✓	✗	✓	✓	✓	✓	✓
Siklos	✓	✗	✓	✓	✓	✗	✗	✓	✓	✗	✓	✗
Sirturo	✗	✓	✓	✗	✓	✓	✗	✗	✗	✗	✓	✓
Soliris	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✗	✓
Sprycel	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Strensiq	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Strimvelis	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗
Sylvant	✗	✓	✗	✗	✓	✓	✗	✗	✓	✗	✓	✗
Tasigna	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
Tepadina	✓	✓	✗	✗	✓	✓	✓	✗	✓	✗	✗	✗
Thalidomide Celgene[e]	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓
Tobi Podhaler	✓	✓	✓	✓	✓	✗	✗	✓	✗	✗	✓	✗
Torisel	✓	✓	✓	✗	✓	✓	✓	✗	✓	✗	✗	✗
Translarna	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✓
Unituxin	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗
Venclyxto	✗	✓	✗	✗	✓	✗	✗	✗	✗	✗	✓	✗
Vidaza	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗
Vimizim	✗	✓	✓	✗	✓	✓	✗	✗	✗	✗	✗	✓
Volibris	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Votubia	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✗
Vpriv	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓
Vyndaqel	✓	✓	✗	✓	✗	✓	✗	✗	✓	✗	✓	✗
Wakix	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗
Xagrid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Xaluprine[f]	✗	✓	✗	✓	✓	✗	✗	✓	✓	✓	✓	✓
Yondelis	✓	✓	✓	✗	✓	✓	✓	✗	✓	✗	✗	✗
Zalmoxis	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Zavesca	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗
number of positive decisions	54	84	69	50	81	47	26	47	56	30	52	29
number of negative decisions	41	11	26	45	14	48	69	48	39	65	43	66

✓, *reimbursement;* ✗, *no reimbursement.*
[a] *Previously Zenas.*
[b] *Previously Para-aminosalicylic acid Lucane.*
[c] *Previously Pomalidomide Celgene.*
[d] *Previously Nymusa.*
[e] *Previously Thalidomide Pharmion.*
[f] *Previously Mercaptopurine Nova Laboratories.*

accessed for data collection are presented in the **Appendix**. For each drug, the information regarding conditional approval or approval under exceptional circumstances was collected from the EMA's website. Then the review of Orphanet database was performed for each drug and corresponding disease targeted by the drug, what revealed that most of orphan drugs were authorized for the treatment of patients with oncologic or metabolic diseases. For that reason, additional analyzes were performed for relevant subgroups of drugs dedicated to the treatment of patients with oncology or metabolic conditions, and a comparison of the results between these 2 subgroups and drugs used for treatment of patients with other diseases (neither oncologic nor metabolic) was made. We focused on drugs for oncologic or metabolic conditions as they are large groups of orphan drugs so justify statistical analysis. Less prevalent groups could be analyzed only descriptively (EMA, 2018).

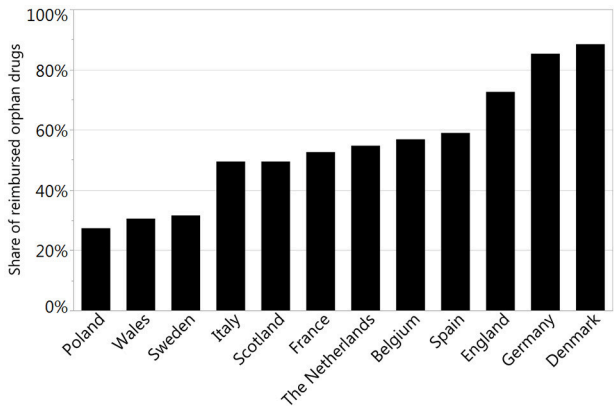

FIGURE 1 | The percentage of reimbursed orphan drugs in selected countries.

Significant differences between reimbursement systems among the countries can impact the comparisons and agreement in recommendations and reimbursement status for the analyzed drugs. The agreement between recommendations and reimbursement decisions for each country separately as well as between countries were assessed using the κ coefficient for measurement of agreement, with values lower than 0 denoting less than chance agreement; between 0.01 and 0.20, slight agreement; between 0.21 and 0.40, fair agreement; between 0.41 and 0.60, moderate agreement; between 0.61 and 0.80, substantial agreement; and between 0.81 and 0.99, almost perfect

TABLE 3 | The relation in reimbursement decisions and type of a disease in selected countries.

Country	Reimbursement	Metabolic diseases	Oncologic diseases	Other diseases	Total	*p*-value (χ^2-test)
Belgium	Not reimbursed	12 (54.55%)	12 (33.33%)	17 (45.95%)	41	0.2597
	Reimbursed	10 (45.45%)	24 (66.67%)	20 (54.05%)	54	
Denmark	Not reimbursed	4 (18.18%)	2 (5.56%)	5 (13.51%)	11	0.2881
	Reimbursed	18 (81.82%)	34 (94.44%)	32 (86.49%)	84	
England	Not reimbursed	3 (13.64%)	14 (38.89%)	9 (24.32%)	26	0.0971
	Reimbursed	19 (86.36%)	22 (61.11%)	28 (75.68%)	69	
France	Not reimbursed	10 (45.45%)	21 (58.33%)	14 (37.84%)	45	0.2105
	Reimbursed	12 (54.55%)	15 (41.67%)	23 (62.16%)	50	
Germany	Not reimbursed	7 (31.82%)	1 (2.78%)	6 (16.22%)	14	0.0097*
	Reimbursed	15 (68.18%)	35 (97.22%)	31 (83.78%)	81	
Italy	Not reimbursed	12 (54.55%)	15 (41.67%)	21 (56.76%)	48	0.3971
	Reimbursed	10 (45.45%)	21 (58.33%)	16 (43.24%)	47	
Poland	Not reimbursed	18 (81.82%)	21 (58.33%)	30 (81.08%)	69	0.0507
	Reimbursed	4 (18.18%)	15 (41.67%)	7 (18.92%)	26	
Scotland	Not reimbursed	14 (63.64%)	17 (47.22%)	17 (45.95%)	48	0.3715
	Reimbursed	8 (36.36%)	19 (52.78%)	20 (54.05%)	47	
Spain	Not reimbursed	11 (50.00%)	10 (27.78%)	18 (48.65%)	39	0.1205
	Reimbursed	11 (50.00%)	26 (72.22%)	19 (51.35%)	56	
Sweden	Not reimbursed	15 (68.18%)	22 (61.11%)	28 (75.68%)	65	0.4082
	Reimbursed	7 (31.82%)	14 (38.89%)	9 (24.32%)	30	
The Netherlands	Not reimbursed	13 (59.09%)	16 (44.44%)	14 (37.84%)	43	0.2821
	Reimbursed	9 (40.91%)	20 (55.56%)	23 (62.16%)	52	
Wales	Not reimbursed	16 (72.73%)	26 (72.22%)	24 (64.86%)	66	0.7376
	Reimbursed	6 (27.27%)	10 (27.78%)	13 (35.14%)	29	
Total	**22**	**36**	**37**	**95**		

**statistically significant.*

TABLE 4 | The agreement in reimbursement decisions between selected countries.

Country	Denmark	England	France	Germany	Italy	Poland	Scotland	Spain	Sweden	The netherlands	Wales
Belgium	0.25 (0.10 to 0.40)	0.30 (0.12 to 0.49)	0.28 (0.09 to 0.47)	0.18 (0.02 to 0.35)	0.47 (0.30 to 0.65)	0.44 (0.30 to 0.59)	0.31 (0.12 to 0.50)	0.57 (0.40 to 0.74)	0.24 (0.07 to 0.41)	0.36 (0.17 to 0.55)	0.14 (0.03 to 0.31)
Denmark		0.19 (−0.01 to 0.40)	0.12 (−0.01 to 0.26)	0.40 (0.14 to 0.67)	0.23 (0.10 to 0.35)	0.09 (0.03 to 0.16)	0.19 (0.06 to 0.31)	0.27 (0.11 to 0.42)	0.11 (0.04 to 0.19)	0.18 (0.04 to 0.32)	0.11 (0.04 to 0.18)
England			0.20 (0.02 to 0.38)	**0.01 (−0.18 to 0.20)**	0.08 (−0.10 to 0.26)	0.21 (0.10 to 0.33)	0.20 (0.03 to 0.38)	0.06 (−0.13 to 0.25)	0.15 (0.02 to 0.28)	0.23 (0.05 to 0.41)	0.14 (0.01 to 0.27)
France				0.23 (0.09 to 0.38)	0.26 (0.07 to 0.46)	0.18 (0.01 to 0.35)	0.47 (0.30 to 0.65)	0.40 (0.22 to 0.59)	0.42 (0.26 to 0.59)	0.41 (0.22 to 0.59)	0.20 (0.02 to 0.37)
Germany					0.21 (0.07 to 0.34)	0.12 (0.05 to 0.19)	0.25 (0.11 to 0.38)	0.30 (0.14 to 0.47)	0.15 (0.06 to 0.23)	0.08 (−0.08 to 0.23)	0.04 (−0.05 to 0.14)
Italy						0.43 (0.27 to 0.59)	0.37 (0.18 to 0.56)	**0.64 (0.49 to 0.79)**	0.22 (0.03 to 0.40)	0.31 (0.12 to 0.50)	0.28 (0.10 to 0.46)
Poland							0.34 (0.17 to 0.51)	0.42 (0.28 to 0.56)	0.29 (0.09 to 0.50)	0.15 (−0.01 to 0.32)	0.16 (−0.05 to 0.36)
Scotland								0.39 (0.21 to 0.57)	0.43 (0.26 to 0.60)	0.47 (0.30 to 0.65)	0.32 (0.15 to 0.50)
Spain									0.25 (0.09 to 0.41)	0.36 (0.17 to 0.55)	0.15 (−0.01 to 0.32)
Sweden										0.35 (0.18 to 0.51)	0.34 (0.13 to 0.54)
The Netherlands											0.17 (−0.01 to 0.34)

κ *coefficients with 95% confidence intervals. The lowest (Germany and England) and the highest (Italy and Spain) values are in bold.*

agreement (Viera and Garrett, 2005). All κ coefficients were supported with 95% confidence intervals (CIs) and rounded to 2 decimal places.

The comparison of 2 nominal variables was performed using the χ^2-test or the Fisher exact test where applicable, depending on expected cell counts in contingency tables. The results of the

TABLE 5 | Relation between reimbursement status and conditional approval.

Country	Conditional approval				*p*-value (χ^2-test)
	No		Yes		
	Not reimbursed	Reimbursed	Not reimbursed	Reimbursed	
Belgium	32 (39.51%)	49 (60.49%)	9 (64.29%)	5 (35.71%)	0.0839
Denmark	9 (11.11%)	72 (88.89%)	2 (14.29%)	12 (85.71%)	0.7318
England	21 (25.93%)	60 (74.07%)	5 (35.71%)	9 (64.29%)	0.4481
France	34 (41.98%)	47 (58.02%)	11 (78.57%)	3 (21.43%)	**0.0113***
Germany	11 (13.58%)	70 (86.42%)	3 (21.43%)	11 (78.57%)	0.4443
Italy	37 (45.68%)	44 (54.32%)	11 (78.57%)	3 (21.43%)	**0.0230***
Poland	57 (70.37%)	24 (29.63%)	12 (85.71%)	2 (14.29%)	0.2344
Scotland	38 (46.91%)	43 (53.09%)	10 (71.43%)	4 (28.57%)	0.0903
Spain	29 (35.80%)	52 (64.20%)	10 (71.43%)	4 (28.57%)	**0.0123***
Sweden	54 (66.67%)	27 (33.33%)	11 (78.57%)	3 (21.43%)	0.3762
The Netherlands	34 (41.98%)	47 (58.02%)	9 (64.29%)	5 (35.71%)	0.1215
Wales	57 (70.37%)	24 (29.63%)	9 (64.29%)	5 (35.71%)	0.6480

**, Bold values—Statistically significant.*

TABLE 6 | Relation between reimbursement status and approval under exceptional circumstances.

Country	Approval under exceptional circumstances				*p*-value (χ^2-test)
	No		Yes		
	Not reimbursed	Reimbursed	Not reimbursed	Reimbursed	
Belgium	32 (39.51%)	49 (60.49%)	9 (64.29%)	5 (35.71%)	0.0839
Denmark	8 (9.88%)	73 (90.12%)	3 (21.43%)	11 (78.57%)	0.2123
England	23 (28.40%)	58 (71.60%)	3 (21.43%)	11 (78.57%)	0.5893
France	37 (45.68%)	44 (54.32%)	8 (57.14%)	6 (42.86%)	0.4276
Germany	8 (9.88%)	73 (90.12%)	6 (42.86%)	8 (57.14%)	**0.0013***
Italy	39 (48.15%)	42 (51.85%)	9 (64.29%)	5 (35.71%)	0.2648
Poland	58 (71.60%)	23 (28.40%)	11 (78.57%)	3 (21.43%)	0.5893
Scotland	40 (49.38%)	41 (50.62%)	8 (57.14%)	6 (42.86%)	0.5919
Spain	31 (38.27%)	50 (61.73%)	8 (57.14%)	6 (42.86%)	0.1850
Sweden	55 (67.90%)	26 (32.10%)	10 (71.43%)	4 (28.57%)	0.7932
The Netherlands	36 (44.44%)	45 (55.56%)	7 (50.00%)	7 (50.00%)	0.6998
Wales	56 (69.14%)	25 (30.86%)	10 (71.43%)	4 (28.57%)	0.8634

**, Bold values—Statistically significant.*

TABLE 7 | Relation between conditional approval, approval under exceptional circumstances, and type of disease.

Disease type	Conditional approval		*p*-value	Approval under exceptional circumstances		*p*-value (χ^2-test)
	No	Yes		No	Yes	
Oncologic	27 (75%)	9 (25%)	0.0323*	34 (94.44%)	2 (5.56%)	0.0227*
Metabolic	22 (100%)	0 (0%)		15 (68.18%)	7 (31.82%)	
Other	32 (86.49%)	5 (13.51%)		32 (86.49%)	5 (13.51%)	

**Statistically significant.*

tests were presented as *p*-values rounded to 4 decimal places. The data were summarized with counts and percentages.

The impact of the EMA's conditional approval as well as approval under exceptional circumstances was assessed using the logistic regression and presented as odds ratio (OR) showing the odds for reimbursement when these types of approval were granted compared with no conditional approval or approval under exceptional circumstances status. Logistic regression was also used to investigate the impact of type of the disease on the type of approval. All ORs were presented with 95% CI rounded to 2 decimal places and corresponding *p*-values rounded to 4 decimal places. A *p*-value of <0.05 was considered statistically significant. Statistical analyzes were carried out in the JMP® software, version 13.1.0 (SAS Institute Inc., 2016, Cary, North Carolina 27513, USA).

RESULTS

Analysis of Reimbursement Decisions for Orphans in Selected Countries

The reimbursement status was assessed for a total of 95 orphan drugs in 12 countries. The percentage of reimbursed drugs varied from 27% in Poland to 88% in Denmark (**Figure 1**). Considering the type of a disease (metabolic/oncologic) a statistically significant relation with the reimbursement status was observed only in Germany (**Table 3**). Regarding the reimbursement status, the highest, substantial agreement was observed between Spain and Italy, and the lowest agreement was detected between Germany and England, with κ of 0.64 and 0.01, respectively (**Table 4**).

The Impact of Conditional Approval and Approval Under Exceptional Circumstances on Reimbursement Status

The conditional approval was associated with reimbursement status only in France, Italy, and Spain. The EMA's conditional approval status in France decreased odds for reimbursement by 80% (OR, 0.20; 95% CI, 0.05–0.76; $p = 0.0185$), in Italy by 77% (OR, 0.23, 95% CI, 0.06–0.88; $p = 0.0324$), and in Spain by 78% (OR, 0.22; 95% CI, 0.06–0.77; $p = 0.0182$) (**Table 5**). Approval under exceptional circumstances was associated with the reimbursement status only in Germany, where the odds for reimbursement were 85% (OR, 0.15; CI 95%, 0.04–0.53; $p = 0.0034$) lower for drugs approved under exceptional circumstances when compared with other drugs (**Table 6**).

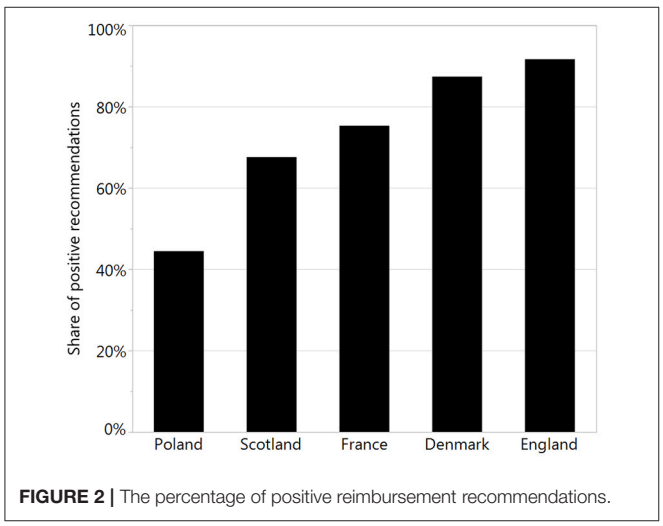

FIGURE 2 | The percentage of positive reimbursement recommendations.

The Impact of Type of Disease on Conditional Approval and Approval Under Exceptional Circumstances

Out of all drugs, 36 (38%) were used for treatment of patients with oncologic diseases (e.g., relapsed or refractory CD30+ Hodgkin lymphoma), 22 (23%) for metabolic diseases (e.g., type 1 Gaucher disease), and 37 (39%) for other diseases (e.g., cystic fibrosis, severe hepatic veno-occlusive disease). Both conditional approval and approval under exceptional circumstances were associated with the type of the disease. Almost one-third of orphan drugs for metabolic diseases were granted approval under the exceptional circumstances compared with only 6% in the case of drugs for oncologic diseases; however, in the case of conditional approval the situation was reversed: a quarter of orphan drugs for oncologic diseases was approved conditionally, compared with 0% of orphan drugs for metabolic diseases (**Table 7**).

Drugs for metabolic diseases were 8.25-fold (95% CI, 1.6–46.90; $p = 0.0123$) more likely to be approved under exceptional circumstances, but had 96% less odds for being conditionally approved (OR, 0.04; 95% CI, 0.00006–0.67; $p = 0.0092$) when compared to other drugs for non-metabolic and non-oncologic diseases. The opposite was observed for drugs used in treatment of patients with oncologic diseases. Those drugs were 87% less likely to be approved under exceptional circumstances (OR, 0.83; 95% CI, 0.01–0.84; $p = 0.0301$) and had the odds for being conditionally approved increased 10-fold (95% CI, 1.58–287.77; $p = 0.006$) when compared with other drugs for non-metabolic and non-oncologic diseases.

Additional Analysis of Recommendations for Orphans in Selected Countries

To perform a sophisticated analysis of recommendations, we made a review of officially available websites and databases and collected relevant data. We found all necessary data only for 5 countries: Denmark, England, France, Poland, and Scotland. The percentage of positive recommendations varied from 44% in Poland to 92% in England (**Figure 2**).

The agreement in recommendation type (negative or positive) was assessed between Denmark, England, France, Poland, and Scotland. For these countries information about positive and negative recommendations was available online. The highest agreement was observed between England and Scotland (κ of 0.54) and the lowest between England and Denmark (insignificant κ of −0.04) (**Table 8**).

TABLE 8 | The agreement in reimbursement recommendations between selected countries.

Country	England	France	Poland	Scotland
Denmark	−0.04 (−0.11 to 0.02)	0.13 (−0.08 to 0.33)	0.00 (0.00 to 0.00)	0.06 (−0.05 to 0.17)
England		0.32 (−0.08 to 0.71)	0.17 (−0.05 to 0.40)	0.54 (0.16 to 0.91)
France			0.16 (−0.07 to 0.39)	0.12 (−0.11 to 0.35)
Poland				0.27 (0.03 to 0.51)

κ *coefficients with 95% confidence intervals.*

The observed agreement between recommendation and the reimbursement status within countries varied from 0.09 (−0.25 to 0.44) in England to 0.7 (0.55–0.96) in Denmark (**Figure 3**).

DISCUSSION

The study investigated the shares of reimbursed orphan drugs among all those with orphan designation among several EU countries and the agreement between them. In addition, to our best knowledge this is the first study that investigates the impact of conditional approval and exceptional circumstances on reimbursement decisions in EU countries.

In France, Italy, and Spain, conditional approval significantly decreased the odds for reimbursement, which suggest that the decision-making body in those countries waits for further data on efficacy or safety (the EMA, after providing conditional approval, requires the applicant to provide further data within the agreed time frame) while in other considered countries the impact of approval status was assessed although not significant. However, a similar association was observed in terms of approval under exceptional circumstances in Germany with the same impact. The observed agreement in reimbursement decisions among the countries varied from agreement on a random level to substantial agreement.

The reimbursement status was significantly associated with the type of the disease (metabolic or oncologic) only for Germany ($p < 0.01$). Taking into account all considered countries the type of disease was however significantly associated with the type of authorization by EMA—drugs for metabolic diseases were 8.25-fold more likely to be approved under exceptional circumstances, oncologic drugs had the odds for being conditionally approved increased 10-fold.

In response to increasing health expenditures, more and more third-party payers tend to rationalize their expenses by implementing cost-effectiveness criterion prior to pricing and reimbursement decisions or at least by referencing pharmaceutical prices of the countries in which evidence on cost-effectiveness are mandated. Objective decision-making for public reimbursement has to be based on clinical and economic criteria, but social issues should also be considered. It is important to note that this study analyzed mostly old (pre-2004) member states of the European Union (EU15) and only one post-2004 accession state (Poland). This may raise some concerns because the comparison was between high-income and low-income countries. However, the results of this study provide a good basis for further research on this subject, especially that the Central Eastern European region has expanded its pharmaceutical share of health spending at an 8-fold higher annual rate compared with EU15 (Jakovljevic et al., 2016). This may result in a faster increase in the share of reimbursed orphan drugs in post-2004 member states. This trend might be then enhanced by new generic versions of orphan drugs that should enter the pharmaceutical market shortly, because patent protection and the exclusivity period for several orphan drugs will expire soon. However, this could raise some concerns as this substitution should be based not only on an economic analysis but also on clinical and patient-reported outcomes (Di Paolo and Arrigoni, 2018). This is particularly important because orphan drugs together with targeted biologics are considered the most expensive types of pharmaceuticals (Jakovljevic and Yamada, 2017).

Financial aspects are the major determinant of the observed differences among the analyzed countries. Many countries apply additional mechanisms to allow access to medicines for which there is high uncertainty (at the time of marketing authorization) regarding effectiveness, cost-effectiveness, or budget impact. These mechanisms are commonly referred to as managed entry agreements (MEAs), that is, negotiations between payers and manufacturers to share the cost of uncertainty. The objective of MEAs is to facilitate access to new and expensive medicines, including orphan drugs.

Various approaches to pricing are another factor that contributed to differences in the availability of orphan drugs. Price revisions are conducted periodically or when necessary, and this varies between countries. In Belgium and Germany, regular revisions may concern only some groups of drugs. Those revisions could be associated with negotiations between the payer and marketing authorization holder (as in France or Italy) or with the planned review of reimbursement decisions after a specific fixed period (as in Poland or the Netherlands) (Panteli et al., 2016).

Drugs for metabolic diseases were more likely to be approved under exceptional circumstances but less likely to be conditionally approved compared with other orphan drugs. This was due to inability to collect comprehensive data on their efficacy and safety. Many drugs for metabolic diseases come as enzyme-replacement therapies, the approval of which may not require comprehensive data on safety. On the other hand, oncologic orphan drugs were more often approved under conditional marketing authorization to provide patients with new drugs as fast as possible even if clinical data were immature or incomplete. However, marketing authorizations holders are

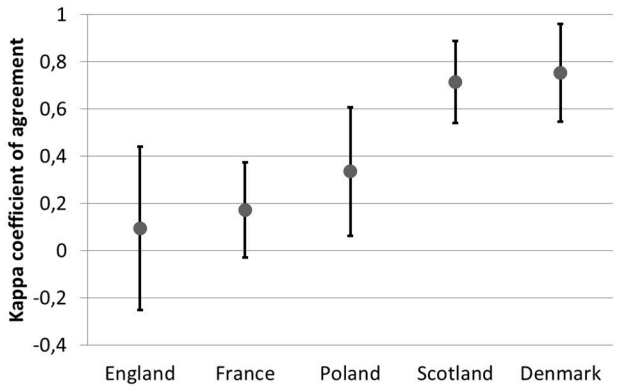

FIGURE 3 | The agreement between recommendations and reimbursement status in the analyzed countries.

obliged to provide relevant data within a defined period to maintain the registration status.

We performed a review on publications for current reimbursement policies in European settings, however no other studies investigated the influence of authorization details on the reimbursement. We reviewed some papers published lately that face the problems. The present study is innovative, as we did not identify valid studies on the similar topic carried out for European countries. A study by Kawalec et al. (2016) had a similar approach, but a revision of methods and an update of input data were necessary to provide the topical and valid review on the management of orphan drugs in the selected European countries. The study revealed that 21% of EMA-authorized orphan drugs were reimbursed in 8 European countries that were studied: 49% of those orphan drugs had positive reimbursement recommendations, 54% of those had conditional reimbursement recommendations, and 16% had negative reimbursement recommendations. The shares of the orphan drugs for oncologic diseases, orphan drugs for ultrarare diseases and other orphan drugs that were assessed by HTA agencies were similar, with the lowest percentage observed in ultra-orphan drugs (72%) and the highest in other orphan drugs (80%). While the highest rate of reimbursement was observed among drugs with positive or conditional recommendation, a high rate of reimbursement (11%) was revealed among ultra-orphan drugs that had never been assessed by any HTA agency (Kawalec et al., 2016). Although methods used in the previous study by Kawalec et al. (2016) seem quite similar, the results are unsuitable for direct comparisons. The orphan drugs varied between this study and the previous one, since in the period between the 2 studies some new drugs were approved as orphans and some drugs failed to maintain the status of orphan drugs. Consequently, a dataset on orphan drugs differed significantly between the previous and present study, which influenced the results and conclusions. In 2015, the study focused on correlations between recommendations and reimbursement decisions in selected countries, while present study focused on the odds of agreement between countries and the impact of special EMA approval modes (conditional approval and approval under exceptional circumstances) on chances for reimbursement.

The percentages of reimbursed orphan drugs were lower in the present study than those observed in other studies (Garau and Mestre-Ferrandiz, 2009; Gammie et al., 2015); as we consider the revealed differences were due different sets of orphan drugs taken under consideration because 3 years ago partly another set of orphan drugs was analyzed. That is why we observed 32% of reimbursed orphan drugs compared to 69% for Sweden however for Scotland the observed percentage of reimbursed orphans 49% was similar to reported 54%.

A comparative analysis on the access to orphan drugs in a sample of Balkan countries −5 EU member states (Bulgaria, Croatia, Greece, Romania, Slovenia) and 2 EU candidate countries (Serbia, Montenegro)—was carried out by Pejcic et al. (2018). It revealed significant inequalities among these countries as well as a substantial lack of access to orphan drugs approved for EU market and a need for improvement in accessibility of orphan drugs in the Balkan states.

Another study was carried out by Sarnola et al. (2018) to assess reimbursement and pricing policies specific to orphan medicines and the availability and distribution settings of 10 recently authorized medicinal products in 24 European countries. No specific policies were implemented in the assessment of reimbursement status of orphan drugs in 22 countries, and in 20 countries no special policies were implemented for pricing. Moreover, the availability of orphan products varied between countries. The authors emphasize the importance of discussing if orphan drugs should be placed in separated group for specific reimbursement regulations to facilitate patient access.

Adkins et al. (2017) made a review to evaluate different mechanisms that have been introduced to facilitate patient access to oncologic orphan drugs in 5 different countries (Australia, Canada, England, France, and Sweden), using 8 oncologic orphan drugs and non-orphan oncologic drugs as examples of their application. It was revealed that additional assessment processes were rarely used and decisions were mostly driven by proving cost-effectiveness using standard incremental cost-effectiveness ratio thresholds. Application of standard HTA criteria to oncologic orphan drugs in many countries does not consider any specificity clinical and cost input producing high cost-effectiveness results (above standard cost-effectiveness thresholds) and HTA agencies should adopt a more flexible approach to cost-effectiveness, considering high unmet medical needs, limited clinical effectiveness evidence but also the small patient numbers involved in therapy with orphan drugs.

A review by Zelei et al. (2016) focused on potentially relevant value drivers in the reimbursement process of orphan drugs. Due to external price referencing of pharmaceuticals, the relative budget impact of orphan drugs is expected to be higher in CEE than in Western European countries unless accessibility of patients remains more limited in poorer European regions. Good clinical evidence seems to play a fundamental role providing an evidence for clinical effectiveness but also input to cost-effectiveness analyzes, which play a key role in decision-making in these countries.

There were substantial differences in the total public expenditure on orphan drugs per capita in participant countries. The absolute spending was clearly associated with the economic status of the countries. The generalizability of the findings may be limited due to several reasons. It should be emphasized that the orphan status of medicines is flexible and can change over time, which considerably influenced the conclusions from the present study compared with the previous results (Orphanet, 2018).

Although our study was planned and conducted so that it was as reliable as possible, it is not free from limitations. First of all, not all European countries were considered in the study and this may introduce some selection bias. We considered only those countries for which the required data were available online. The results should be interpreted in the context of analyzed countries and may not be generalizable to the EU as a whole; however, the results can be generalizable to other potential orphan drugs, which constitute the evident strength of the study. In addition, the differences in decision-making processes between the analyzed countries resulted in the lack of data for recommendations for some of them.

Additionally, collection of data from different websites is prone to errors hence there is a great need of the unified system to bring together relevant data for reimbursed drugs for all EU member states.

The κ coefficient with 95% CI was used to analyze the agreement in reimbursement statuses between countries as well as the agreement between reimbursement recommendations and statuses within countries. To our knowledge, this is the best approach; however, it could be influenced by the presence of bias between countries and by the distributions of reimbursement statuses. Hence, the presented coefficients should be treated as descriptive statistics rather than an inference. The agreement as well as predictive abilities of conditional approval and approval under exceptional circumstances could be confounded by other factors that were not analyzed in this study such as results of economic analyzes, reliability of clinical trials of specific drugs, or experts' opinions.

Despite some limitations the study have several strengths: a comprehensive analysis for eligible countries with different reimbursement systems was performed, considering all orphan drugs approved in the EU; it's a novelty as no such studies were conducted before. Results of the study would be useful for reimbursement decision making and orphan drug policies in European countries as international comparisons and review of reimbursement statuses in other states could be an important aspect providing simpler and faster evaluation of orphan drug value. The results of this study should constitute a good basis for further research.

CONCLUSIONS

The percentage of reimbursed orphan drugs varied among the countries and was the lowest in Poland and the highest in Denmark. The highest, substantial agreement in reimbursement decisions was observed between Italy and Spain, and the highest agreement in recommendations was observed between England and Scotland. The conditional approval significantly decreased the chance for reimbursement in France, Italy, and Spain. The approval granted under the exceptional circumstances had the same impact only in Germany. Drugs for metabolic diseases were more likely to be approved under exceptional circumstances, but had lesser odds for being conditionally approved when compared to other drugs for non-metabolic and non-oncologic diseases. The opposite was observed for drugs used in treatment of patients with oncologic diseases.

AUTHOR CONTRIBUTIONS

PK developed the concept, designed and coordinated the study. PK and KM analyzed the data and wrote the draft of the manuscript. PK, WT, CS, and AP wrote the final version of the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX—LIST OF REFERENCE WEBSITES

Poland (http://www.mz.gov.pl, http://www.aotm.gov.pl)
England (https://www.england.nhs.uk, https://www.nice.org.uk)
Scotland (http://www.isdscotland.org, https://www.scottishmedicines.org.uk)
Sweden (https://www.tlv.se)
Wales (www.wales.nhs.uk, http://www.awmsg.org)
Germany (https://www.dimdi.de, https://www.g-ba.de)
France (http://solidarites-sante.gouv.fr, https://www.has-sante.fr)
The Netherlands (https://www.gipdatabank.nl)
Denmark (http://www.medicinpriser.dk, https://laegemiddelstyrelsen.dk)
Belgium (http://www.inami.fgov.be)
Spain (https://www.vademecum.es)
Italy (http://www.aifa.gov.it)

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(miejscowość, data)

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OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trabka W, Sowada C, Pilc A. Reimbursement of Orphan Drugs in Europe in Relation to the Type of Authorization by the European Medicines Agency and the Decision Making Based on Health Technology Assessment. Front Pharmacol. 2018 Nov 12;9:1263. doi: 10.3389/fphar.2018.01263

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
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Refundacja leków na choroby rzadkie (leki sieroce) jest głównym czynnikiem wpływającym na ich dostępność dla pacjentów. Refundacja jest poprzedzona autoryzacją danego leku, która w przypadku leków sierocych odbywa się w procedurze centralnej przeprowadzanej przez EMA, która może wydać autoryzację w trzech trybach: bez dodatkowych warunków, autoryzacja warunkowa, która wymusza dostarczenie dodatkowych danych najczęściej dotyczących skuteczności lub bezpieczeństwa po określonym czasie oraz autoryzacja na zasadach specjalnych, która dopuszcza, iż część danych może być niemożliwa do zgromadzenia, np. z powodów etycznych. Rodzaj autoryzacji może być powiązany zarówno z rodzajem choroby, w terapii której dany lek ma być stosowany jak również z decyzjami dotyczącymi jego refundacji w różnych krajach.

Celem niniejszego opracowania była ocena i porównanie odsetka refundowanych leków sierocych pomiędzy krajami członkowskimi UE z regionu CEE tj. Bułgarii, Chorwacji, Czechach, Estonii, Litwie, Łotwie, Polsce, Rumunii, Słowacji i na Węgrzech oraz ocena zgodności w podejmowaniu decyzji refundacyjnych pomiędzy analizowanymi krajami. Dodatkowo ocenie podlegał związek rodzaju autoryzacji EMA z typem choroby leczonej danym lekiem i decyzjami refundacyjnymi w analizowanych krajach. Dokonany został również wyczerpujący przegląd polityki refundacyjnej w odniesieniu do leków sierocych w analizowanych krajach.

Zaobserwowano, iż odsetek refundowanych leków sierocych w krajach CEE waha się od 6.4% na Łotwie do 27.4% w Polsce i nie zależy od PKB per capita. Największa zgodność w decyzjach refundacyjnych została zaobserwowana pomiędzy Estonią i Litwą (κ=0.69), natomiast najmniejsza pomiędzy Estonią i Łotwą (κ=0.11). Zarówno rodzaj autoryzacji jak i typ choroby były istotnie powiązane z decyzjami refundacyjnymi w niektórych z analizowanych krajów, z których większość przyjęła odrębne przepisy refundacyjne dotyczące leków sierocych.

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ORIGINAL RESEARCH
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Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries

Krzysztof Piotr Malinowski[1], Paweł Kawalec[1], Wojciech Trąbka[2], Marcin Czech[3], Guenka Petrova[4], Manoela Manova[4,5], Alexandra Savova[4,5], Pero Draganić[6,7], Lenka Vostalová[8], Juraj Slabý[8], Agnes Männik[9], Kristóf Márky[10], Zinta Rugaja[11], Jolanta Gulbinovic[12], Tomas Tesar[13] and Marian Sorin Paveliu[14]*

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Background: Reimbursement policies influence access of patients to orphan drugs in the European countries.

Objectives: To provide a comprehensive description of orphan drug reimbursement policies and to assess reimbursement decision-making process in the EU-CEE countries as well as the impact of the type of approval and disease on reimbursement decisions.

Methods: For each drug, the information regarding conditional approval or approval under exceptional circumstances was obtained from the EMA website. The reimbursement status for analyzed drugs was collected in a questionnaire survey performed in a group of experts in reimbursement policy. The agreement between countries was assessed using the κ coefficient, nominal variables tests were compared using the $\chi 2$ test or the Fisher exact test. The impact of the EMA's conditional approval and approval under exceptional circumstances was assessed using logistic regression and presented as an odds ratio (OR).

Results: The analysis revealed that most orphan drugs were authorized for the treatment of oncological or metabolic diseases [36 drugs (38%) and 22 drugs (23%), respectively]. The shares of reimbursed orphan drugs varied significantly ($p = 0.0031$) from 6.3% in Latvia to 27.4% in Poland. No correlation ($r = 0.02$; $p = 0.9583$) with GDP per capita was observed. The highest agreement in reimbursement decisions was observed between Estonia and Lithuania, and the lowest – between Estonia and Latvia, with kappa of 0.69 and 0.11, respectively. Significant impact of the type of approval and reimbursement status was observed for Czechia, Lithuania

and Slovakia where conditional approval and exceptional circumstances negatively influenced reimbursement decision. Type of disease has significant influence on reimbursement decision in 4 out of 10 analyzed countries with significant outweigh of positive decisions for oncological diseases.

Conclusion: In considered countries specific regulations on reimbursement of orphan drugs are valid but in Lithuania and Romania no formal HTA process was employed; in case of some countries higher ICER values for orphans are used. The share of reimbursed orphan drugs varied significantly across the countries, but it was not associated with GDP per capita.

Keywords: orphan drug, reimbursement policy, Central and East Europe, European Medicine Agency, kappa coefficient of agreement, marketing authorisation, exceptional circumstances, conditional approval

INTRODUCTION

Rare diseases mostly include inherited life-threatening or chronically debilitating diseases that affect fewer than 5 out of 10,000 people, according to the definition issued by the European Medicines Agency (EMA), however, the definition can vary between countries. This results in an approximate number of 246,000 patients affected by rare diseases in 27 European Union (EU) member countries (European Medicines Agency, 2007; Winstone et al., 2015). Reimbursement of drugs for rare diseases (so-called orphan drugs – approved by centralized procedure) is the most important factor that can increase the accessibility of treatment for patients. The EMA provides three types of approval: (a) conditional – a temporary approval until more data from clinical trials are available and the conditions will be fulfilled; (b) exceptional circumstances – a status that indicates that it is not possible to obtain additional data; and (c) approval without additional conditions (European Commission, 2006; European Medicines Agency, 2018a). Unlike the conditional approval, in which a marketing approval is granted on condition that a sponsor will provide relevant data within an agreed time frame, authorization under exceptional circumstances can be granted even when the more precise data will not be available for a more comprehensive assessment - usually data are further collected via registries instead of clinical trials. In all situations, the benefit of the product should outweigh the risk.

Both conditional approval and exceptional circumstances could influence reimbursement decision-making and should be considered in reimbursement policies, especially in countries with a limited budget (European Commission, 2006), such as the member states that joined the EU in 2004 as mostly middle- and low-income countries from the Central Eastern European (CEE) region. The situation has gradually improved for these countries, as they have expanded their pharmaceutical shares of health spending at an 8-fold higher annual rate compared with the 15 original EU countries (EU15; Jakovljevic et al., 2016). Orphan drugs along with targeted biologics are considered the most expensive pharmaceuticals (Jakovljevic and Yamada, 2017); therefore, it is especially important to improve their availability in CEE countries. Proper allocation of public resources represents a major challenge for public health and health care decision-making and seems to be reflected in substantial differences in reimbursement decisions for orphan drugs among the EU15 countries (Malinowski et al., 2018).

There are different classes of orphan drugs, with the broadest classes including oncological drugs [around 32.5% of orphan drugs (Gammie et al., 2015)] and drugs for metabolic conditions.

Our objective of this study was to assess and compare the percentage of reimbursed orphan drugs as well as the agreement in reimbursement decision-making between selected CEE countries. We also aimed to evaluate if reimbursement decisions were influenced by whether the EMA granted conditional approval or approval under exceptional circumstances. The impact of the type of disease (oncological or metabolic) on the type of approval (conditional or under exceptional circumstances) was also examined. Overall, we aimed to provide a comprehensive review of reimbursement policies for orphan drugs in EU–CEE countries.

MATERIALS AND METHODS

For each drug, the information regarding conditional approval or approval under exceptional circumstances was obtained from the EMA website (European Medicines Agency, 2018b). The reimbursement status for selected drugs was collected in a questionnaire survey performed in a group of experts in reimbursement policy and orphan drugs in the following EU-CEE countries: Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia in 2017–2018. Data on the reimbursement system and decision-making process in these countries were also collected. Additional analyses were performed for the relevant subgroups of drugs used in the treatment of patients with oncological or metabolic conditions. Finally, the results for these two subgroups of drugs were compared with drugs used for the treatment of patients with other diseases (neither oncological nor metabolic; European Medicines Agency, 2018b).

The agreement (share of agreed answers over the expected at random) between countries was assessed using the κ coefficient, with values lower than 0 denoting less than chance agreement; between 0.01 and 0.20, slight agreement; between 0.21 and 0.40, fair agreement; between 0.41 and 0.60, moderate agreement;

between 0.61 and 0.80, substantial agreement; and between 0.81 and 0.99, almost perfect agreement (Viera and Garrett, 2005). All κ coefficients were supported with 95% confidence intervals (CIs) and rounded to 2 decimal places.

Two nominal variables were performed using the χ^2 test or the Fisher exact test, as applicable, depending on expected cell counts in contingency tables. The results of the tests were presented as *p*-values rounded to 4 decimal places. The data were summarized with counts and percentages.

The impact of the EMA's conditional approval and approval under exceptional circumstances was assessed using logistic regression and presented as an odds ratio (OR) showing the odds for reimbursement when these types of approval were granted compared with no conditional approval or approval under exceptional circumstances. Logistic regression was also used to investigate the impact of the type of disease on positive reimbursement decisions. All ORs were presented with 95% CIs rounded to 2 decimal places and with corresponding *p*-values rounded to 4 decimal places. A *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were carried out in the JMP® software, version 14.0.0 (SAS Institute Inc., 2018, Cary, NC, United States).

RESULTS

The reimbursement status of 95 orphan drugs was assessed. The analysis revealed that most orphan drugs were authorized for the treatment of patients with oncological or metabolic diseases (36 drugs (38%) and 22 drugs (23%), respectively; **Table 1**]. The shares of reimbursed orphan drugs varied significantly (*p*-value of 0.0031) from a minimum of 6.3% in Latvia to a maximum of 27.4% in Poland (**Figure 1**). We observed that the shares of reimbursed orphan drugs experienced a trend with the total gross domestic product (GDP; correlation of 0.53), although the result was not significant (*p*-value of 0.1185). Additionally, no correlation (correlation of 0.02; *p*-value of 0.9583) was observed when analyzing GDP per capita (**Figure 1**).

Comparative Summary of Orphan Drug Reimbursement Policy

Half of analyzed countries implemented special regulations regarding (including different sources of payment or relaxed reimbursement requirements like higher thresholds) the reimbursement of orphan drugs. In most countries, the marketing authorization holder (MAH) applies for reimbursement of a particular drug; however, in Estonia and Lithuania, applications by doctors' or patients' organizations are also possible. Reimbursement decisions are made mostly by bodies responsible for health policies in individual countries, e.g., ministries of health (MoH). In some countries, other bodies are also included in the reimbursement decision-making process. In all analyzed countries the list of reimbursed drugs is publicly available (**Table 2**).

A full or simplified health technology assessment (HTA) of a submitted application should be performed with reimbursement application in most analyzed countries except Romania and Lithuania. In Romania, the system is based on score cards that consider the reimbursement status of a particular drug in other countries (United Kingdom, Germany, and France), and in Lithuania there is a formal HTA process implemented but it does not include economic assessment. This is why in some of those countries HTA is limited to the assessment of clinical data in other it also includes analysis of cost-effectiveness, e.g., ICER and/or quality-adjusted life year (QALY; or Life Years Gained – LYG). In all other countries ICER providing information on marginal cost per QALY is employed in reimbursement decision-making, but no higher threshold value is implemented for orphan drugs compared with non-orphan drugs (**Table 3**).

The Agreement in Reimbursement Decisions

The highest agreement in reimbursement decisions was observed between Estonia and Lithuania, and the lowest – between Estonia and Latvia, with kappa coefficients of 0.69 and 0.11, respectively. In all pairwise comparisons the agreement was higher than 0; however, in a few pairs the lower bound of the confidence interval was negative, which indicated that there was no observed agreement in reimbursement decisions between those countries (Czechia and Romania, Estonia and Latvia, Estonia and Romania, Hungary and Romania, Romania and Slovakia; **Table 4**).

Reimbursement Decisions in the Context of the Type of Authorization and Disease

In total, 14 drugs (14.74%) were approved conditionally and another 14 drugs (14.74%) were approved under exceptional circumstances. The type of authorization was associated with the type of disease (*p*-value of 0.0053). Medicinal products for the treatment of genetic metabolic disorders were usually authorized under exceptional circumstances, and oncological drugs – under conditional approval (**Table 5**).

The reimbursement status was significantly associated with the type of approval only in the Czechia, Lithuania, and Slovakia. In those countries no drugs approved conditionally were reimbursed (out of all analyzed drugs – other conditionally approved drugs could be reimbursed like Erivedge for advanced basal cell carcinoma was in The Czechia); however, in other countries at least one drug that was conditionally approved was reimbursed. In Lithuania, Slovakia, and Latvia, no drugs approved under exceptional circumstances were reimbursed – however, they may be available on patient bases, because of rarity of the disorder (**Table 6**).

The relationship between the type of disease and the reimbursement status was significant in Croatia, Estonia, Hungary, and Lithuania (**Table 7**). In all those countries, most reimbursed drugs were indicated for the treatment of oncological diseases. Logistic regression supports these results and in Croatia, oncological orphan drugs were more than five times more likely to be reimbursed compared with the remaining drugs (OR of 5.33; 95%CI: 1.31–21.68; *p*-value of 0.0124). In Estonia the odds for reimbursement were 90% lower for metabolic than for other orphan drugs (OR of 0.10; 95%CI: 0.01–0.82; *p*-value of 0.0314).

TABLE 1 | Reimbursement status of orphan drugs in 10 Central Eastern European Countries in 2017.

Medicine name	Drug type	Common name	Conditional approval	Exceptional circumstance	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Adcetris	Oncological	Brentuximab vedotin	Yes	No	✓	✓	×	✓	✓	×	×	✓	×	×
Adempas	Other	Riociguat	No	No	×	×	✓	✓	×	×	✓	✓	✓	×
Alprolix	Other	Eftrenonacog alfa	No	No	×	×	×	✓	×	×	×	×	×	×
Arzerra	Oncological	Ofatumumab	No	No	✓	✓	×	×	×	×	×	×	✓	✓
Atriance	Oncological	Nelarabine	No	Yes	✓	×	×	×	✓	×	×	✓	✓	×
Blincyto	Oncological	Blinatumomab	Yes	No	×	×	×	×	×	×	×	×	×	×
Bosulif	Oncological	Bosutinib	Yes	No	✓	✓	×	✓	✓	✓	×	✓	✓	×
Bronchitol	Other	Mannitol	No	No	×	×	×	✓	×	×	×	×	×	×
Carbaglu	Metabolic	Carglumic acid	No	No	×	×	×	×	×	×	×	×	✓	×
Cayston	Other	Aztreonam	No	No	×	×	×	×	×	×	×	×	×	×
Ceplene	Oncological	Histamine dihydrochloride	No	Yes	×	×	×	×	×	×	×	×	×	×
Cerdelga	Metabolic	Eliglustat	No	No	×	×	×	×	×	×	×	×	×	×
Coagadex	Metabolic	Human coagulation factor X	No	No	×	×	×	×	×	×	×	×	×	×
Cometriq	Oncological	Cabozantinib	Yes	No	×	×	×	×	×	×	×	×	×	×
Cresemba	Other	Isavuconazole	No	No	×	×	×	×	×	×	×	×	×	×
Cystadane	Metabolic	Betaine anhydrous	No	No	×	×	×	×	×	×	×	✓	✓	×
Dacogen	Oncological	Decitabine	No	No	×	×	×	×	×	×	×	×	✓	×
Darzalex	Oncological	Daratumumab	Yes	No	×	×	×	×	×	×	×	×	×	×
Defitelio	Other	Defibrotide	No	Yes	×	×	×	×	×	×	×	×	×	×
Deltyba	Other	Delamanid	Yes	No	×	×	×	×	×	×	×	×	×	×
Diacomit	Other	Stiripentol	No	No	×	×	✓	✓	×	×	✓	✓	✓	×
Elaprase	Metabolic	Idursulfase	No	Yes	✓	✓	✓	×	×	×	×	✓	✓	×
Esbriet	Other	Pirfenidone	No	No	×	×	✓	✓	✓	×	✓	✓	×	×
Farydak	Oncological	Panobinostat	No	No	×	×	×	×	×	×	×	×	×	×
Firazyr	Other	Icatibant	No	No	×	×	✓	×	✓	×	×	✓	×	×
Firdapse (previously Zenas)	Other	Amifampridine	No	Yes	×	×	×	×	×	×	×	×	×	×
Galafold	Metabolic	Migalastat	No	No	×	×	×	×	×	×	×	×	×	×
Gazyvaro	Oncological	Obinutuzumab	No	No	×	✓	✓	×	✓	✓	✓	✓	×	✓
Gliolan	Oncological	5-aminolevulinic acid hydrochloride	No	No	×	×	×	×	×	×	×	×	×	×
Glybera	Metabolic	Alipogene tiparvovec	No	Yes	×	×	×	×	×	×	×	×	×	×
Granupas (previously para-aminosalicylic acid Lucane)	Other	Para-aminosalicylic acid	No	No	×	×	×	×	×	×	×	×	×	×

(Continued)

TABLE 1 | Continued

Medicine name	Drug type	Common name	Conditional approval	Exceptional circumstance	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Hetlioz	Other	Tasimelteon	No	No	×	×	×	×	×	×	×	×	×	×
Holoclar	Other	*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells	Yes	No	×	×	×	×	×	×	×	×	×	×
Iclusig	Oncological	Ponatinib	No	No	×	×	×	×	×	×	×	×	×	✓
Idelvion	Other	Albutrepenonacog alfa	No	No	×	×	×	×	×	×	×	×	×	×
Imbruvica	Oncological	Ibrutinib	No	No	✓	×	×	✓	✓	×	✓	✓	×	✓
Imnovid (previously pomalidomide Celgene)	Oncological	Pomalidomide	No	No	×	×	✓	×	×	×	×	×	×	×
Increlex	Metabolic	Mecasermin	No	Yes	×	×	✓	×	×	×	×	✓	×	×
Inovelon	Other	Rufinamide	No	No	×	×	✓	×	✓	×	×	×	×	✓
Kalydeco	Metabolic	Ivacaftor	No	No	×	×	×	×	×	×	×	×	×	×
Kanuma	Metabolic	Sebelipase alfa	No	No	×	×	×	×	×	×	×	×	×	×
Ketoconazole HRA	Metabolic	Ketoconazole	No	No	×	×	×	×	×	×	×	×	×	×
Kolbam	Metabolic	Cholic acid	No	Yes	×	×	×	×	×	×	×	×	×	×
Kuvan	Metabolic	Sapropterin	No	No	✓	×	✓	✓	×	×	×	×	✓	✓
Kyprolis	Oncological	Carfilzomib	No	No	×	×	×	×	×	×	×	×	×	×
Lartruvo	Oncological	Olaratumab	Yes	No	×	×	×	×	×	×	×	×	×	×
Lenvima	Oncological	Lenvatinib	No	No	×	×	×	×	×	×	×	×	×	×
Lynparza	Oncological	Olaparib	No	No	✓	✓	×	✓	×	×	✓	✓	×	×
Mepact	Oncological	Mifamurtide	No	No	×	×	✓	✓	×	×	×	×	×	×
Mozobil	Other	Plerixafor	No	No	✓	✓	✓	×	✓	✓	×	✓	✓	×
Nexavar	Oncological	Sorafenib	No	No	✓	✓	✓	✓	✓	×	✓	✓	×	✓
NexoBrid	Other	Concentrate of proteolytic enzymes enriched in bromelain	No	No	×	×	×	×	×	×	×	×	×	×
Ninlaro	Oncological	Ixazomib	Yes	No	×	×	×	×	×	×	×	×	×	×
Nplate	Other	Romiplostim	No	No	✓	✓	✓	×	✓	✓	×	×	✓	✓
Ocaliva	Other	Obeticholic acid	Yes	No	×	×	×	×	×	×	×	×	×	×
Ofev	Other	Nintedanib	No	No	×	×	✓	✓	✓	×	✓	×	×	×
Onivyde	Oncological	Irinotecan hydrochloride trihydrate	No	No	×	×	×	×	×	×	×	×	×	×
Opsumit	Other	Macitentan	No	No	×	×	×	×	✓	×	×	✓	×	✓
Orphacol	Metabolic	Cholic acid	No	Yes	×	×	×	×	×	×	×	×	×	×

(Continued)

TABLE 1 | Continued

Medicine name	Drug type	Common name	Conditional approval	Exceptional circumstance	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Peyona (previously Nymusa)	Other	Caffeine	No	No	✓	×	×	×	×	×	×	×	✓	×
Plenadren	Metabolic	Hydrocortisone	No	No	×	×	×	×	×	×	×	×	×	×
Procysbi	Other	Mercaptamine	No	No	×	×	×	×	×	×	×	×	×	×
Ravicti	Metabolic	Glycerol phenylbutyrate	No	No	×	×	×	×	×	×	×	×	×	×
Raxone	Other	Idebenone	No	Yes	×	×	×	✓	×	×	×	×	×	×
Revestive	Other	Teduglutide	No	No	×	×	×	×	×	×	×	×	×	×
Revlimid	Oncological	Lenalidomide	No	No	×	✓	✓	✓	✓	×	✓	✓	×	✓
Scenesse	Metabolic	Afamelanotide	No	Yes	×	×	×	×	×	×	×	×	×	×
Signifor	Metabolic	Pasireotide	No	No	✓	×	×	×	×	×	×	×	✓	✓
Siklos	Other	Hydroxycarbamide	No	No	×	×	×	×	×	×	×	×	×	×
Sirturo	Other	Bedaquiline	Yes	No	✓	×	×	×	×	×	×	×	×	×
Soliris	Other	Eculizumab	No	No	×	×	×	×	×	×	×	×	×	×
Sprycel	Oncological	Dasatinib	No	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Strensiq	Metabolic	Asfotase alfa	No	Yes	×	×	×	×	×	×	×	×	×	×
Strimvelis	Other	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	No	No	×	×	×	×	×	×	×	×	×	×
Sylvant	Other	Siltuximab	No	No	×	×	×	×	×	×	×	×	×	×
Tasigna	Oncological	Nilotinib	No	No	✓	×	✓	✓	✓	✓	✓	✓	✓	✓
Tepadina	Oncological	Thiotepa	No	No	×	×	×	×	×	×	×	✓	×	×
Thalidomide Celgene (previously Thalidomide Pharmion)	Oncological	Thalidomide	No	No	×	×	×	✓	✓	×	✓	×	✓	×
Tobi Podhaler	Other	Tobramycin	No	No	✓	×	✓	✓	×	×	✓	×	×	✓
Torisel	Oncological	Temsirolimus	No	No	✓	×	✓	×	✓	×	×	✓	×	✓
Translarna	Other	Ataluren	Yes	No	×	×	×	×	×	×	×	×	×	×
Unituxin	Oncological	Dinutuximab	No	No	×	×	×	×	×	×	×	×	×	×
Venclyxto	Oncological	Venetoclax	Yes	No	×	×	×	×	×	×	×	×	×	×
Vidaza	Oncological	Azacitidine	No	No	✓	×	✓	✓	×	×	✓	✓	×	✓
Vimizim	Metabolic	Elosulfase alfa	No	No	×	×	×	×	×	×	×	×	×	×
Volibris	Other	Ambrisentan	No	No	✓	×	✓	✓	✓	×	✓	✓	✓	✓

(Continued)

TABLE 1 | Continued

Medicine name	Drug type	Common name	Conditional approval	Exceptional circumstance	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Votubia	Oncological	Everolimus	No	No	✓	×	×	✓	×	×	✓	✓	✓	×
Vpriv	Metabolic	Velaglucerase alfa	No	No	×	×	✓	×	×	×	×	✓	×	✓
Vyndaqel	Other	Tafamidis	No	Yes	✓	×	×	×	×	×	×	×	✓	×
Wakix	Other	Pitolisant	No	No	×	×	×	×	×	×	×	×	×	×
Xagrid	Other	Anagrelide	No	Yes	×	×	×	✓	×	×	×	×	×	×
Xaluprine (previously Mercaptopurine Nova Laboratories)	Oncological	Mercaptopurine	No	No	✓	×	✓	✓	✓	×	×	×	×	×
Yondelis	Oncological	Trabectedin	No	No	×	×	×	×	×	×	×	✓	✓	×
Zalmoxis	Oncological	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Yes	No	×	×	×	×	×	×	×	×	×	×
Zavesca	Metabolic	Miglustat	No	No	✓	×	✓	×	×	×	×	×	×	✓

✓ – reimbursed; × – not reimbursed.

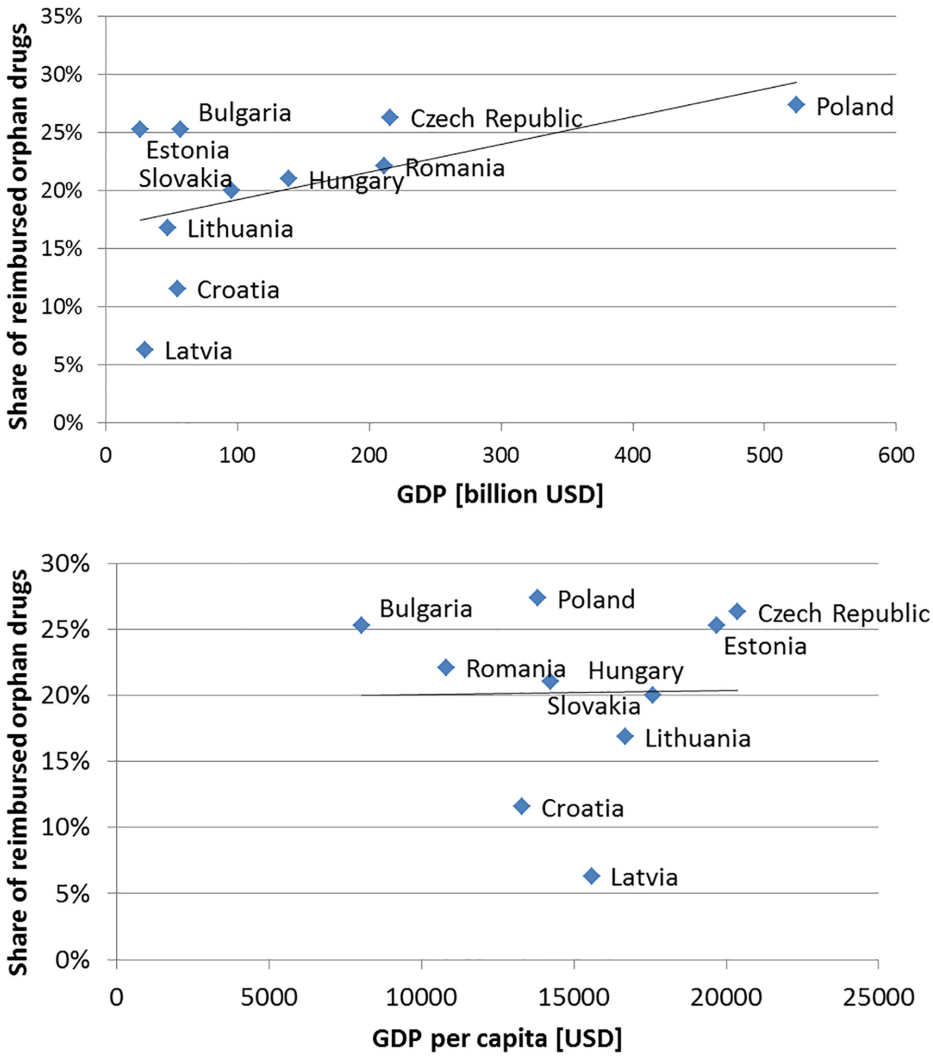

FIGURE 1 | Relationship between share of reimbursed orphan drugs among analyzed countries and total gross domestic product (GDP) and GDP per capita with trend line.

Reimbursement Policy in Analyzed Countries

In Bulgaria, the reimbursement requirements for orphan drugs are the same as for other medicinal products; the initiative for reimbursement is only by MAH. The National Council on Prices and Reimbursement of Medicinal Products is responsible for the final decision about the reimbursement and the level of reimbursement. Most orphan drugs are paid from the budget of the National Health Insurance Fund, but some are paid from hospital budgets. Orphan drugs need to be included in Annex I (or Annex II) of the publicly available Positive Drug List. The reimbursement level depends on the type of disease, type of treatment (essential, symptomatic, palliative, or other), and budget resources allocated for procurement of the medicinal product. The level or reimbursement for orphan drugs is usually 100% or, in some rare cases, 75%. In the process of reimbursement, the decision-maker performs an additional assessment based on the severity of a rare condition, the availability of an alternative product, and the cost for the patient if the medicinal product is not reimbursed. The process also considers if the drug has an orphan status which mean the drug has a great social benefit and their use is indicated for serious conditions for which there is no effective alternative therapy. For Bulgaria, the ICER value is not published in normative documents such as regulations and law. The National Council on prices and reimbursement has published methodological recommendations on documentation presented for assessment of the efficacy, safety and pharmacoeconomic parameters of medicinal products applying for inclusion in the Positive Drug List. The pharmacoeconomic analysis shall indicate whether the medicinal product is cost-effective using the World Health Organization's CHOICE programme (Choosing Interventions that are Cost-Effective). The result must be presented as GDP in Bulgarian currency and in the purchasing power standard

TABLE 2 | Summary of reimbursement aspects in Central Eastern European countries.

Question	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Are there any special laws /policies regarding orphan drugs different from the ones for non-orphan drugs?	No	Yes	No	No	Yes	No	Yes*	No	Yes	Yes
If yes, could you please describe in what way the special law/policy for orphan drugs differ from that for non-orphan drugs?	NA	Source of payment	NA	NA	e.g., acceptability of cost-effectiveness	NA	Positive decision of The Ultra-rare diseases reimbursement Committee	NA	Special therapeutic programs	No QALY thresholds
Who (or what entity) provides reimbursement decisions (decisions on the coverage of a part or whole cost of orphan drugs from public budget)?	The National Council for Pricing and Reimbursement of Medicinal Products	CHIF	SUKL	Ministry of Social Affairs, Health Insurance Fund	NIHIFM, Department of HTA, HTA Committee, Ministry of Human Capacities	The National Health Service of Latvia or Committee	Reimbursement committee or Ultra-rare diseases reimbursement Committee	MoH	Drug Agency evaluation, MoH, NHIH	MoH
Is the list of reimbursed drugs publicly available?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Who applies for reimbursement? Is it the MAH or a public decision-making body, e.g., the MoH?	MAH	MAH	MAH, importer, domestic manufacturer, health insurance company	MAH, doctors' organizations	MAH	MAH, authorized representative, wholesaler	MAH, doctors' or patients' organizations, doctor application for an individual patient (ultra-rare disease)	MAH	MAH	MAH

MAH, Marketing Authorization Holder; MoH, Ministry of Health; QALY, Quality-Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio; GDP, Gross Domestic Product; CEA, Cost-Effectiveness Analysis; CUA, Cost-Utility Analysis; CMA, Cost-Minimization Analysis; BIA, Budget Impact Analysis; NA, Not Applicable; HTA, Health Technology Assessment; SUKL, State Institute for Drug Control in the Czechia; NHIH, National Health Insurance House in Romania; CHIF, Committee for Medicines in Croatia; NIHIFM, National Institute of Health Insurance Fund Management. "" indicates ultra-orphan (1:200,000) diseases.*

(adjusted by the purchasing power parity), according to official data published by the National Statistical Institute (**Tables 2**, **3**).

In Croatia, drugs for rare diseases are delivered through hospitals. There is a special fund (part of the Croatian Health Insurance Fund [CHIF]) for orphan drugs. The reimbursement of these drugs will not burden a hospital budget. Orphan drugs included in the essential list of drugs of the CHIF are completely reimbursed, while those included in the additional list are partially reimbursed. During the reimbursement application process, a budget impact analysis should be provided. A cost-effectiveness analysis, a clinical analysis, or an expert opinion can be additionally provided if needed. The ICER value is important or even essential in the reimbursement decision; in some cases, there is a need to provide additional budget impact analysis results (**Tables 2**, **3**).

In The Czechia, the State Institute for Drug Control (a governmental regulatory agency) decides on pricing and reimbursement of drugs used in outpatient (ambulatory) care. However, SUKL does not decide on drugs used in in-patient (hospital) care. These drugs are reimbursed from hospital budgets (based on agreements between hospitals and health insurance funds). In the context of orphan medicines, it is important to note that if any medicine is not approved to be reimbursed from any reason, it can still be reimbursed on individual patient request if this is the only treatment available for the individual patient taking account of his/her clinical state. In this case, the reimbursement of this medicine needs to be pre-approved by the patient's health insurance fund. Several entities could apply for reimbursement: a MAH (for authorized medicinal products), an importer or domestic manufacturer (for foods for special medical purposes or non-registered medical products used in the Czechia within a specific treatment program), and health insurance companies. The budget impact analysis is required in the HTA process, and the cost-effectiveness analysis is required in most cases. In some cases, a similar efficacy and safety profile of applicant drug in relation to comparators make a cost-minimization analysis possible. HTA analyses are required in all cases when reimbursement conditions are broadened (such as new indications, fewer restrictions on target patient groups) in comparison with the current state or a therapeutically interchangeable intervention. The ICER value is important in decision-making except for temporary reimbursement applications granted for a minimum of 2 years, renewable for another year. Usually, medicines with temporary reimbursement are highly innovative products (i.e., new medicines for very serious diseases with an unmet medical need). The current legislation does not define a threshold for ICER. However, during the HTA process, the State Institute for Drug Control compares the ICER of the assessed technology with the ICERs of already reimbursed technologies (used for similar indications or similar patient groups). The usual ICER used in line with the institute's decision-making practice is 1.2 million CZK per QALY (about 44,500 EUR per QALY; **Tables 2**, **3**).

Estonia has not implemented special reimbursement legislation for orphan drugs. For all drugs reimbursement decisions are performed by the Ministry of Social Affairs and the funding is provided by the Health Insurance

TABLE 3 | Summary of health technology assessment aspects in Central Eastern European countries.

Question	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania*	Poland	Romania	Slovakia
What HTA analyses should be provided during the reimbursement application process (e.g., cost-effectiveness analysis, budget impact analysis, clinical analysis, etc.)?	**Clinical analysis, CEA/CUA, BIA, ethical considerations.**	**BIA, CEA, clinical analysis, expert opinion**	**BIA, CEA/CUA, clinical analysis**	**Full HTA dossier required for orphan drugs**	**Full economic evaluation (CEA/CUA, BIA)**	**Clinical analysis, price analysis, CEA/CMA, BIA**	**No formal HTA process; however, clinical analysis, CEA/CUA, BIA should be provided.**	**CEA/CUA/CMA, BIA, clinical analysis, rationalization analysis**	**Score cards**	**Clinical analysis, CEA/CUA, BIA**
Is ICER value important in reimbursement decision-making?	Yes	Yes	Yes	Yes.	Yes	Yes	NA	Yes	No	Yes
Are there any thresholds for ICER valid in reimbursement decision-making in your country?	No	Yes	No	No	Yes	Yes	NA	Yes	No	Yes
Is there another (higher) ICER threshold for orphan drugs?	No	No	No	No	No	No	NA	No	No	NA

MAH, Marketing Authorization Holder; MoH, Ministry of Health; QALY, Quality-Adjusted Life Year; ICER, Incremental Cost-Effectiveness Ratio; GDP, Gross Domestic Product; CEA, Cost-Effectiveness Analysis; CUA, Cost-Utility Analysis; CMA, Cost-Minimization Analysis; BIA, Budget Impact Analysis; NA, Not Applicable; HTA, Health Technology Assessment; SUKL, State Institute for Drug Control in the Czechia; NHIH, National Health Insurance House in Romania; CHIF, Committee for Medicines in Croatia; NIHIFM, National Institute of Health Insurance Fund Management. "" indicates ultra-orphan (1:200,000) diseases.*

TABLE 4 | Kappa coefficients of agreement in reimbursement status of analyzed drugs among Central Eastern European countries.

Country	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Bulgaria	0.42 (0.21–0.64)	0.37 (0.16–0.58)	0.39 (0.18–0.60)	0.41 (0.20–0.62)	0.26 (0.05–0.46)	0.31 (0.09–0.53)	0.40 (0.20–0.61)	0.51 (0.30–0.71)	0.49 (0.28–0.70)
Croatia		0.27 (0.06–0.48)	0.22 (0.00–0.43)	0.43 (0.20–0.66)	0.55 (0.26–0.84)	0.27 (0.02–0.52)	0.39 (0.18–0.59)	0.26 (0.03–0.49)	0.30 (0.06–0.54)
Czechia			0.42 (0.22–0.63)	0.51 (0.30–0.71)	0.25 (0.05–0.44)	0.48 (0.27–0.69)	0.49 (0.29–0.69)	0.20 (−0.02–0.41)	0.53 (0.33–0.73)
Estonia				0.41 (0.20–0.62)	**0.11 (−0.07–0.29)**	**0.69 (0.51–0.86)**	0.40 (0.20–0.61)	0.21 (−0.00–0.43)	0.25 (0.03–0.47)
Hungary					0.40 (0.17–0.64)	0.45 (0.23–0.68)	0.54 (0.35–0.74)	0.22 (−0.00–0.45)	0.45 (0.23–0.67)
Latvia						0.20 (−0.05–0.45)	0.23 (0.04–0.42)	0.30 (0.08–0.53)	0.25 (0.01–0.48)
Lithuania							0.52 (0.32–0.72)	0.23 (0.00–0.46)	0.41 (0.17–0.64)
Poland								0.35 (0.14–0.56)	0.34 (0.12–0.55)
Romania									0.18 (−0.05–0.40)

The highest and lowest agreements are marked bold.

Fund. Only MAH or doctors' organizations can apply for reimbursement, and a full HTA dossier is required for orphan drugs. However, ICER is important in the decisions-making process not specific threshold are defined neither for orphan nor non-orphan drugs.

In Hungary, there is no separate legislation for orphan drugs; however, some policies apply particularly to this drug class, such as acceptability of cost-effectiveness or importance of the role of equity. One of the entities that can apply for the reimbursement of an orphan drug is an HTA committee established by the National Institute of Health Insurance Fund Management. The other route is through the Ministry of Human Capacities: the National Institute sends a recommendation on drug reimbursement to the Ministry; for new active substances, it is necessary to amend the law for the reimbursement (e.g., in the case of a new indication). The Ministry is in charge of the amendment. In most cases, the representative of the MAH, but sometimes the MAH itself, applies for a reimbursement dossier. The value of ICER is a very important criterion, but there are more criteria that must be considered such as equity, budget impact, or the disease severity. The ICER cannot be higher than 3 times the GDP per capita; however, there is no separate threshold for orphan drugs (**Tables 2**, **3**).

Latvia does not have any special legislation regarding orphan drugs. Orphan medicines are partially available via the positive reimbursement list; some orphans are available as a part of the special programme of rare diseases for Children's University Hospital, Riga. Some orphan drugs are provided within individual reimbursement with limitation up to 14,228.72 euro/year for a single patient. The reimbursement process is started by the holder of a registration certificate, an authorized representative, or a wholesaler by submitting by submitting a full dossier. If orphan drugs are submitted to be reimbursement in the Positive list or individual reimbursement the decision is made by The National Health Service of Latvia. If an orphan drug is used to treat the very rare disease the decision is made by the Committee. In all cases, the applicant should provide clinical, cost-effectiveness, and the budget impact analyses. The ICER value is important in the decision-making process. The calculation of the costs for one unit of an additionally obtained result of therapeutic efficacy (ICER), the coefficient of expansion of cost-effectiveness for a life-year gained or a progression-free survival do not exceed the three times the GDP per capita. The economic analysis also takes into account the proof of the cost-effectiveness of the medicinal products in the health care system at large or for a specific group of patients (**Tables 2**, **3**).

Lithuania implemented separate legislation for orphan drugs for very rare diseases. Only a drug used for an ultra-rare disease (defined in Lithuania as a disease or human health condition with one newly diagnosed case per 200,000 inhabitants per year) can be reimbursed. If orphan drugs are applicable to be reimbursement in the Positive list the decision is made by the Reimbursement committee. If an orphan drug is used to treat the ultra-rare disease the decision is made by The Ultra-rare diseases reimbursement Committee according to the doctor's application. The MAH, as well as doctors' or patients'

TABLE 5 | Relationship between type of the disease and type of approval in European Union.

Disease type	Conditional Approval	Exceptional Circumstances	Unconditional	Total	*p*-value (FET)
Metabolic	0 (0.00%)	7 (31.82%)	15 (68.18%)	22	0.0053*
Oncological	9 (25.00%)	2 (5.56%)	25 (69.44%)	36	
Other	5 (13.51%)	5 (13.51%)	27 (72.97%)	37	
Total	14	14	67	95	

p-value less than 0.05 is marked with an asterisk. FET, Fisher Exact Test.

TABLE 6 | Relationship between reimbursement status and type of approval in Central Eastern European countries.

Country	Reimbursement status	Conditional Approval	Exceptional Circumstances	Unconditional	Total	*p*-value
Bulgaria	Reimbursed	3 (12.50%)	3 (12.50%)	18 (75.00%)	24	0.8568
	Not reimbursed	11 (15.49%)	11 (15.49%)	49 (69.01%)	71	
Croatia	Reimbursed	2 (18.18%)	1 (9.09%)	8 (72.73%)	11	0.8279
	Not reimbursed	12 (14.29%)	13 (15.48%)	59 (70.24%)	84	
Czechia	Reimbursed	0 (0.00%)	2 (8.00%)	23 (92.00%)	25	0.0161*
	Not reimbursed	14 (20.00%)	12 (17.14%)	44 (62.86%)	70	
Estonia	Reimbursed	2 (8.33%)	2 (8.33%)	20 (83.33%)	24	0.2817
	Not reimbursed	12 (16.90%)	12 (16.90%)	47 (66.20%)	71	
Hungary	Reimbursed	2 (10.00%)	1 (5.00%)	17 (85.00%)	20	0.2506
	Not reimbursed	12 (16.00%)	13 (17.33%)	50 (66.67%)	75	
Latvia	Reimbursed	1 (16.67%)	0 (0.00%)	5 (83.33%)	6	0.5744
	Not reimbursed	13 (14.61%)	14 (15.73%)	62 (69.66%)	89	
Lithuania	Reimbursed	0 (0.00%)	0 (0.00%)	16 (100.00%)	16	0.0179*
	Not reimbursed	14 (17.72%)	14 (17.72%)	51 (64.56%)	79	
Poland	Reimbursed	2 (7.69%)	3 (11.54%)	21 (80.77%)	26	0.3704
	Not reimbursed	12 (17.39%)	11 (15.94%)	46 (66.67%)	69	
Romania	Reimbursed	1 (4.76%)	3 (14.29%)	17 (80.95%)	21	0.3264
	Not reimbursed	13 (17.57%)	11 (14.86%)	50 (67.57%)	74	
Slovakia	Reimbursed	0 (0.00%)	0 (0.00%)	19 (100.00%)	19	0.0070*
	Not reimbursed	14 (18.42%)	14 (18.42%)	48 (63.16%)	76	
Total		14	14	67	95	

p-values less than 0.05 are marked with an asterisk.

organizations, could apply for reimbursement of orphan drugs. However, in the case of drugs for ultra-rare diseases, only the doctor's application for reimbursement for an individual patient is acceptable. Reimbursement may depend on the prevalence of the disease (orphan drug vs. oncology drug) and on the application (there may be that the MAH has not applied for reimbursement). The HTA process in Lithuania is not implemented yet, but in its application for a drug to be included in the positive list, the MAH should provide clinical, cost-effectiveness, and the budget impact analyses. If doctors apply to the Committee for reimbursement of drugs used for ultra-rare disease, they should provide information on the patient's clinical condition and substantiation of orphan drug use (**Tables 2**, **3**).

Poland does not implement any separate legislation for orphan drugs, which are treated as ordinary medications. However, such drugs could be reimbursed for individual patients. If it is the case an approval is granted by the Ministry of Health, a drug is financed from a hospital budget. Multi-criteria decision analysis (MCDA) is considered as a strategic direction indicating an additional element in the decision-making process for orphan drugs reimbursement in Poland (Ministry of Health, 2019). The key policy maker and the regulator in the health care system in Poland is the Ministry of Health, supported by advisory bodies. The AOTMiT is an independent legal entity that collects data and delivers statements and recommendations on technologies claiming public funding, of which predominant are drugs. The Transparency Council, which is an independent advisory body consisting of 20 highly qualified members providing opinions for applicant drugs. The final reimbursement decisions are taken independently by the Minister of Health, and the decisions do not have to comply with statements or recommendations issued by the Transparency Council or the President of the AOTMiT. Poland implements external reference pricing, internal reference pricing, value-based pricing and negotiations when establishing price of drugs (**Tables 2**, **3**).

TABLE 7 | Relationship between reimbursement status and type of rare disease in analyzed Central Eastern European countries.

Country	Reimbursement status	Metabolic	Oncological	Other	Total	*p*-value
Bulgaria	Reimbursed	4 (16.67%)	13 (54.17%)	7 (29.17%)	24	0.1639
	Not reimbursed	18 (25.35%)	23 (32.39%)	30 (42.25%)	71	
Croatia	Reimbursed	1 (9.09%)	8 (72.73%)	2 (18.18%)	11	0.0403*
	Not reimbursed	21 (25.00%)	28 (33.33%)	35 (41.67%)	84	
Czechia	Reimbursed	5 (20.00%)	10 (40.00%)	10 (40.00%)	25	0.9069
	Not reimbursed	17 (24.29%)	26 (37.14%)	27 (38.57%)	70	
Estonia	Reimbursed	1 (4.17%)	13 (54.17%)	10 (41.67%)	24	0.0259*
	Not reimbursed	21 (29.58%)	23 (32.39%)	27 (38.03%)	71	
Hungary	Reimbursed	0 (0.00%)	12 (60.00%)	8 (40.00%)	20	0.0104*
	Not reimbursed	22 (29.33%)	24 (32.00%)	29 (38.67%)	75	
Latvia	Reimbursed	0 (0.00%)	4 (66.67%)	2 (33.33%)	6	0.2306
	Not reimbursed	22 (24.72%)	32 (35.96%)	35 (39.33%)	89	
Lithuania	Reimbursed	0 (0.00%)	10 (62.50%)	6 (37.50%)	16	0.0231*
	Not reimbursed	22 (27.85%)	26 (32.91%)	31 (39.24%)	79	
Poland	Reimbursed	4 (15.38	15 (57.69	7 (26.92	26	0.0507
	Not reimbursed	18 (26.09%)	21 (30.43%)	30 (43.48%)	69	
Romania	Reimbursed	5 (23.81%)	9 (42.86%)	7 (33.33%)	21	0.8194
	Not reimbursed	17 (22.97%)	27 (36.49%)	30 (40.54%)	74	
Slovakia	Reimbursed	4 (21.05%)	10 (52.63%)	5 (26.32%)	19	0.3043
	Not reimbursed	18 (23.68%)	26 (34.21%)	32 (42.11%)	76	
Total		22	36	37	95	

p-values less than 0.05 are marked with an asterisk.

The case of Romania is fundamentally different, orphan drugs being included in a therapeutic program for the rare disease. MAH submits the file of the product to the National Drug and Medical Device Agency (NDMDA). The evaluation consists mainly of allocating to every drug several points for its reimbursement status in the United Kingdom, Germany, and France. Orphan drugs are receiving a bonus score comparative with other molecules. This is so called Score cards method. The Government approves the NDMDA's recommendation through a Government Decision published in the *Official Gazette of Romania*. After issuing a therapeutic protocol for the new drug the reimbursed status becomes effective by the National Health Insurance House (NHIH) and MoH jointly order (**Tables 2**, **3**).

Slovakian reimbursement decisions were in 2017 based on thresholds (commonly described with the Greek letter "λ") set forth by Act No. 363/2011 Z. z. The lower threshold (λ1) was defined as 24 times the average monthly salary (21,192 EUR/QALY), and the upper threshold (λ2), as 35 times the average monthly salary (30.905 EUR/QALY). The medicine was reimbursed from public health insurance (fully or partially) if the incremental costs were lower or equal to λ1 per one QALY. The medicine was conditionally reimbursed if the incremental costs lied within λ1 and λ2 thresholds per one QALY. Medicinal products whose additional costs per QALY exceeded the upper λ2 threshold should not be included in the reimbursement list. These thresholds were not applicable for orphan drugs indicated for therapy of rare diseases with prevalence lower than 1:100,000 in Slovakia.

Based on the new Slovak legislation (updated Act No. 363/2011 Z. z.), which came into the force in January 1st 2018, Slovakian reimbursement decisions was in 2018 based on the following thresholds:

- lower threshold (λ1): 35 times average monthly salary (total 31.920 EUR/QALY);
- upper threshold (λ2): 41 times average monthly salary (total 37.392 EUR/QALY).

In general, the medicine is reimbursed from public health insurance (fully or partially) if the incremental costs were lower or equal to λ1 per one incremental QALY. In defined cases could be the thresholds per one incremental QALY increased up to λ2.

Based on the Slovak legislation, which came into the force in January 1, 2018, the cost – effectiveness thresholds were not used in 2018 for medicines in the following cases: an applicant do not need to attach a pharmacoeconomic analysis for the decision making procedure at the Slovak Ministry of Health concerning to reimbursement from the public health fund in the case that a medicinal product is aimed for treatment of disease, for which the number of patients eligible for treatment with the medicinal product based on the indication approved in marketing authorization was in the Slovak republic lower than 1: 50,000.

The required dossiers obligatory in reimbursement procedures should be submitted by the MAH and have to include basic drug information, evidence on its effectiveness, the standard therapeutic dose, and the number of standard therapeutic doses per package. Applications also contain the

proposed reimbursement rate, indication, and restriction of prescription and/or indication, if applicable.

After a medicine receives market authorization, the Ministry of Health of the Slovak Republic determines its maximum retail price (ex-factory price), applying external reference pricing methodology. The final price of each medicine available on the Slovak pharmaceutical market may not exceed the average of the three lowest prices of the same medicine available on pharmaceutical markets across the EU. The Slovak Ministry of Health established the Reimbursement (or Categorization) Committee to act as its advisory body on reimbursement processes. The Committee prepares recommendations for reimbursement levels, patients' co-payments, and conditions for reimbursement. The decision about the reimbursement levels of eligible medicines is based on the following criteria: therapeutic benefit of the medicine; cost-effectiveness; and the reimbursed levels of other medicines within the same reference group. The final reimbursement (or categorization) list also includes medicines with prescription or indication restrictions. In the case of certain oncological medicines, the reimbursement can also be restricted to prescription solely in specialized hospitals. Based on the recommendations from the Categorization Committee the Ministry of Health issues final decisions (**Tables 2**, **3**).

DISCUSSION

The objective of this study was to provide a comprehensive description of orphan drug reimbursement policies in EU–CEE countries. Moreover, we aimed to assess the agreement in reimbursement decisions between those countries as well as the impact of the type of approval and disease (oncological or metabolic) on reimbursement decisions. We observed that half of the analyzed countries imposed specific regulations regarding reimbursement of orphan drugs; however, none of the countries used higher an ICER threshold (marginal costs per QALY) for orphan drugs. The share of reimbursed orphan drugs varied significantly across the countries; however, it was not significantly associated with neither GDP not GDP per capita. The agreement between the countries varied from slight agreement (Estonia vs. Latvia) to substantial agreement (Estonia vs. Lithuania); however, the agreement was also affected by the different shares of reimbursed orphan drugs. Our study revealed that there are differences in reimbursement and HTA policies across so called Baltic countries. In Lithuania no formal HTA process has been implemented; in Latvia no special laws or policies regarding orphan drugs different from the ones for non-orphan drugs are in force; in Lithuania the special policies apply only to ultra-orphan drugs (defined as indicated for illnesses with a prevalence of 1:200,000 or lower). The differences between those countries could be also noticed from the perspective of burden of healthcare on households' budgets. The financial burden of paying for medicines in 2017 in EU countries varied significantly with Estonia being one of the countries with the smallest share of households with high burden and Latvia and Lithuania being one of the countries with the highest share of households with high burden (European Commission, 2019).

In The Czechia, Lithuania and Slovakia, the reimbursement statuses were significantly associated with the type of approval; while in Croatia, Estonia, Hungary and Lithuania, the type of disease was significantly associated with the reimbursement status. In all those countries, most reimbursed drugs were indicated for the treatment of oncological diseases.

In some countries limitations in reimbursement only for some subgroups of patients due to budgetary constraints are applicable; public coverage is limited only for patients fulfilling some inclusion criteria e.g., stage or severity of disease.

To compare the results of our study with current knowledge on the subject, we performed a systematic review of publications in medical databases. We identified a study from 2016 by Zelei et al. (2016), who reviewed scientific evidence on the HTA of orphan drugs with a special focus on public payers in CEE countries. The authors observed that only 5 of 87 publications included in the analysis referred to CEE countries, which indicates the need for further research. As CEE countries are more budget-restricted than western countries, they could be more affected by the lack of clinical evidence for orphan drugs, which generally gain marketing authorization earlier than non-orphan drugs. Our present study showed that the type of marketing authorization plays an important role in many CEE countries. If the accessibility of orphan drugs remains at the same level in the CEE region as in western EU countries, the relative budget impact could be significantly higher.

The study from 2012 by Iskrov et al. (2012) focused on the perspective on Bulgaria in terms of reimbursement of orphan drugs. The authors revealed that of all 61 orphan drugs approved in the EU in 2011, only 16 were available in Bulgaria and the mean waiting time for reimbursement decision was 43 months (standard deviation, 29 months). Similarly, to our study, the author emphasized the need for special legislation for orphan drugs that are not only based on epidemiological but, more importantly, on economic factors for better assets allocation.

Pavlović et al. (2012) revealed that in 2012 in Bulgaria the Positive Drug List included 44.3% (27 out of 61) of the drugs with prior orphan designation, as compared with only 25% (17 out of 68) in Serbia and 52.5% (32 out of 61) in Sweden, which also indicated a difference between Eastern and Western part of Europe.

Logviss et al. (2014) evaluated a situation in Latvia in 2014. They revealed that 34 orphan drugs were available in Latvia, although only three were reimbursed (all indicated for Philadelphia chromosome–positive chronic myeloid leukemia). Additionally, 15 drugs (44.1%) were reimbursed for individual patients and another five drugs (14.7%) were reimbursed as part of a medical treatment program for rare diseases in children.

Picavet et al. (2012) analyzed access to orphan drugs for almost all EU countries (except for Cyprus, Malta, and Portugal) based on data from IMS Health (2011). They showed that employing an HTA process plays an important role in the patients' access to reimbursed orphan drugs, which mostly affect low-GDP countries. However,

nowadays more low-GDP countries use a formal HTA process than in 2011.

Gammie et al. (2015) analyzed regulations and policies used by countries to allow patient access to orphan drugs in 2015 by performing a systematic review of evidence published between 1998 and 2014. They summarized legislations of 35 countries from around the world, including 21 from the EU, and revealed that a different type of special regulations for orphan drugs (national orphan drug policies, orphan drug designation, marketing authorization, marketing exclusivity, and tax credits) was present in most of the countries. A variation in the share of orphan drugs accessible for the patients was also observed.

Kamusheva et al. (2018) provided a comprehensive description of access of patients with rare diseases to biotechnological drugs in several CEE countries in 2018, showing that special legislation for orphan drugs was implemented in several CEE countries. The share of accessible orphan drugs as well as total expenditures varied across countries, being the highest in Greece and the lowest in Romania.

Szegedi et al. (2018) revealed that from 29.4 to 92.8% of the 83 orphan drugs were available (and reimbursed) in 2015 in 8 EU countries in favor of the higher-income ones. The highest expenditure on orphan drugs in the years from 2013 to 2014 was observed in Belgium (245–280 million Euro) and the lowest in Bulgaria (8.3–12.2 million Euro).

Another study assessed Bulgarian legislation on HTA and reimbursement decision-making criteria, with a special focus on orphan and innovative drugs. A critical analysis of current decision-making criteria for drug reimbursement was performed, and a comprehensive assessment scoring system for orphan drugs with decision-making criteria was scheduled, including the presence of therapeutic alternative, clinical effectiveness, safety, pharmacoeconomics, and societal value, which were divided into weighted indicators. The study revealed that Bulgarian reimbursement decision-making seems not to be sufficiently transparent and not effective in innovative HTA, with access to a therapeutic alternative as a key reimbursement decision-making criterion for orphan drugs (Iskrov et al., 2013).

In the recent study Czech et al. (2018) compared rare disease definitions and epidemiology, diagnostics and new-born screening, national plans, patient registries and reimbursement of orphan drugs including HTA processes in Poland, Russia, and the Netherlands. There are clear differences in healthcare expenditure and rare disease policies between these countries. Access to reimbursed orphan drugs varies widely between these three countries, and sometimes even within (Russia). Budgeting structures (i.e., federal vs. regional) play a large role in regional healthcare access for patients, especially in Russia, where local government institutions and budgets often determine the type and level of healthcare provided. These findings were confirmed in our analyses.

In our previous study (Malinowski et al., 2018) we have analyzed orphan drugs reimbursement policies in selected Western European countries. We have observed that the share of reimbursed orphan drugs is significantly higher in Western Europe than in the CEE states however, the agreement between countries has not present any spatial relationship as in the current study. In both studies we have observed a significant influence of both disease type and EMA drug authorization type on reimbursement decisions in some countries - conditional approval significantly decreased the chance for reimbursement in France, Italy, and Spain by 77–80%; approval granted under exceptional circumstances had significant impact only in Germany with 85% decrease in chances for reimbursement. The different shares of reimbursed drugs between previous and current studies (which is an obvious finding) make comparisons of results of both projects difficult.

Our study is the first to comprehensively analyse of the impact of the type of EMA approval and the type of the disease on orphan drug reimbursement decision-making, which constitutes the major strength of this study. The results should aid orphan drug management and policies in a number of countries, including CEE countries. The current and updated review of reimbursement decisions among countries and international comparisons provide additional input for proper and effective reimbursement decision-making. Moreover, we collected the data in cooperation with a number of local experts familiar with reimbursement policy in each country, so the input is worthwhile and credible. There is an institutional regional cooperation initiative worth mentioning based on a memorandum of understanding signed by selected CEE countries called V4+ Fair and Affordable Pricing. Its ultimate goal is to develop and harmonize methods of cooperation and negotiations with MAHs concerning pricing and conditions for reimbursement of selected health technologies with a special emphasis on the highest priced drugs including orphan medicinal products. The objective is to build an active institutional network, exchange of expertise and experience in pricing and reimbursement and conduct common health technology assessment aimed at facilitation access to effective and affordable treatment solutions. In our study we not only did the regulation analysis but measure the regulatory agreement, as well as also try to find its possible correlation with other factors as GDP of the countries. We have applied κ coefficient to measure the extent of agreement between countries that is above the random (at chance). In addition, we used logistic regression to calculate odds for positive reimbursement decision in association with the type of the disease. Using those statistical methods is inevitable strength of the study.

Our study has also some limitations. First of all, we analyzed drugs with orphan designations granted in 2017. We also collected data valid for 2017 due to changes in reimbursement systems in included countries, so our results will need an update in the coming years. Moreover, a constant monitoring of reimbursement statuses in analyzed countries, with conclusions on current trends in reimbursement decision-making for orphan drugs would be especially beneficial - so the issue needs further assessment and additional studies. Chances for reimbursement in analyzed countries could be also affected by the prevalence of the diseases, which should be tested during further studies.

CONCLUSION

The study revealed that some of the considered countries already established separate regulations on reimbursement of orphan drugs; in case of some of these countries higher ICER values for orphans are used; in Lithuania and Romania, no formal HTA process was employed. The share of reimbursed orphan drugs varied significantly across the countries, but it was not associated either with GDP or GDP per capita. The lowest (slight) agreement in reimbursement decisions was observed between Estonia and Latvia, and the highest (substantial) agreement, between Estonia and Lithuania. In The Czechia, Lithuania and Slovakia, EMA's conditional approval significantly decreased the chances for reimbursement. In Croatia, Estonia, Hungary, and Lithuania, drugs for oncological diseases had significantly greater chances for reimbursement.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

KM performed the data synthesis and analysis as well as drafted the manuscript. PK designed and supervised the study, and wrote the final manuscript. WT supervised the study and critically reviewed the manuscript. MC contributed to review the manuscript and wrote the final version of the manuscript. GP, MM, AS, PD, LV, JS, AM, KM, ZR, JG, TT, and MP provided necessary data and wrote country-specific sections of the manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Lublin 03.11.2020
(miejscowość, data)

dr. hab. Paweł Kawalec, prof. UM
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
koncepcja i projekt pracy, opracowanie metodologii i krytyczna korekta opracowania.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez Krzysztofa Malinowskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych. Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład Krzysztofa Malinowskiego przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Kawalec Paweł
(podpis wnioskodawcy)

Kraków, 03.11.2020
(miejscowość, data)

Dr hab. Wojciech Trąbka
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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Wojciech Trąbka
(podpis wnioskodawcy)

W-we 8.11.2020
(miejscowość, data)

PROF. MARCIN CZECH
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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Marcin Czech
(podpis wnioskodawcy)

Bulgaria, Sofia, 3.11.2020
(place/city, date)

Prof. Guenka Petrovaq PhD, DSci
(degree, name and surname)

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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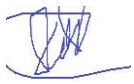

G. Petrova
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Sofia 06.11.2020
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Prof. Mariela Manova, PhD
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STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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Bulgaria, Sofia, November 5, 2020.
(place/city, date)

Prof. Alexandra Savova, PhD
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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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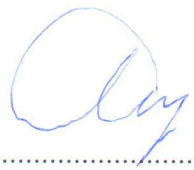

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Zagreb, 5. November 2020.

Associate Professor, MD, PhD, Pero Draganić

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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Brno, 11.11.2020
(place/city, date)

PharmDr. Lenka Vostálová, Ph.D.
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STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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Lenka Mlady
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Prague, 03.11.2020

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STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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London, 19th Nov 2020
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Agnes Männik MSc, PG Cert
(degree, name and surname)

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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A Männik
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KRISTÓF MÁRKY
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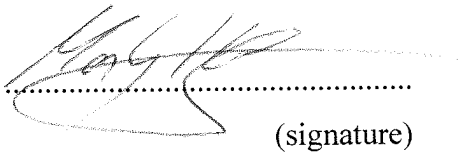

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Riga, 03.11.2020.
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Ziuter Rugaja
(degree, name and surname)

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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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(signature)

Vilnius, 04-11-20202

…….....

(place/city, date)

Dr. Jolanta Gulbinovič

.....

(degree, name and surname)

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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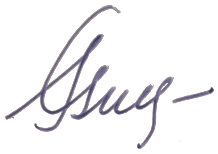

.....

(signature)

Slovakia, Bratislava, November 03, 2020

Assoc. Prof. Tomas Tesar, PharmDr., PhD, MBA

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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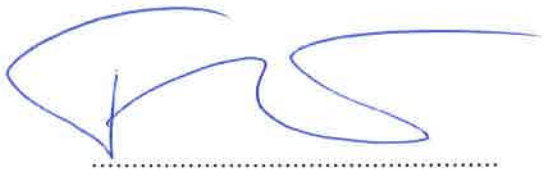

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Asoc. Prof. dr. Sorin Paveliu
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Usv. Ștefan Maiorescu
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Bucharest Romania

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Czech M, Petrova G, Manova M, Savova A, Draganić P, Vostalová L, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Reimbursement Legislations and Decision Making for Orphan Drugs in Central and Eastern European Countries. Front Pharmacol. 2019 May 8;10:487. doi: 10.3389/fphar.2019.00487.

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(signature)

Publikacja 3:

Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9.

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Choroba przewlekła/zagrażająca życiu o rozpowszechnieniu <5 przypadków na 10,000 osób definiowana jest jako choroba rzadka, a około jednej trzeciej z nich to schorzenia onkologiczne. Refundacja leków sierocych w celu zwiększenia ich dostępności dla pacjenta jest szczególnym wyzwaniem w krajach UE z regionu CEE, gdyż leki te należą do jednych z najdroższych technologii medycznych. Wdrożenie procesu HTA jest w tym obszarze również szczególnie istotne. Tematyka ta, że dość często badania, jednakże nie istnieje dostateczna analiza sytuacji podgrupy leków sierocych stosowanych w schorzeniach onkologicznych – tak zwanych onkologicznych leków sierocych w krajach UE-CEE.

Celem niniejszej pracy było przeprowadzenie analizy procesu formułowania rekomendacji HTA w krajach UE-CEE oraz porównanie odsetka onkologicznych leków sierocych, które otrzymały pozytywną rekomendację HTA oraz tych, które ostatecznie zostały refundowane. Oceniona została również zgodność pomiędzy rekomendacją HTA a statusem refundacyjnym leku oraz wydatki z budżetów państw UE-CEE na refundację onkologicznych leków sierocych.

Badanie wykazało, że organizacja procesu HTA w krajach UE-CEE nie jest jednolita, zaobserwowano, iż w niektórych krajach pozytywna rekomendacja HTA wiąże się z refundacją, co może się przekładać, na zmienność w odsetku rekomendowanych onkologicznych leków sierocych od 11% na Łotwie do 36% w Bułgarii i Estonii oraz odsetku tych, które zostały refundowane od 11% na Łotwie do 42% w Polsce. Najmniejsza zgodność pomiędzy rekomendacją HTA a statusem refundacyjnym została zaobserwowana w Polsce (κ=0.4) a największa na Łowie, Węgrzech i Słowacji (κ=1). Wydatki z budżetu państwa na refundację analizowanych leków były dodatnio skorelowane z całkowitym PKB kraju, lecz nie z PKB per capita.

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Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe

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Abstract

Background: The reimbursement of orphan drugs (OD) is an increasingly important for country policymakers, and still insufficiently understood, especially in Central and Eastern Europe. The aim of this research was to provide a comprehensive description of country-specific health technology assessment (HTA) policies as well as evaluate the percentage of HTA recommendations and reimbursement decisions for oncology OD. In addition, the study was designed to elucidate the impact of reimbursement of these drugs on the public budget and the agreement between HTA recommendations and reimbursement decisions in the analysed countries. A questionnaire survey was used to collect data on the reimbursement status, HTA recommendation, marketing authorisation, and public expenses on reimbursement in 2014, 2015, and 2016 for all oncology drugs with an orphan designation by the European Medicine Agency in 2017 in Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia. The agreement between the HTA recommendation and reimbursement status was assessed using the kappa coefficient. The Pearson's correlation was used to analyse the relationship between gross domestic product (GDP) and GDP per capita and reimbursement expenses.

Results: A total of 36 drugs were analysed (25% conditionally approved; 5.56% approved under exceptional circumstances). The share of reimbursed drugs ranged from 11.11% in Latvia to 41.67% in Poland. The highest share of positive recommendations was observed for Bulgaria and Estonia (36.11%), and the lowest, for Latvia (11.11%). The agreement varied from 0.4 for Poland to 1 for Latvia, Hungary, and Slovakia. Expenses were correlated with GDP (0.95 [0.81–0.99]), and not with GDP per capita (0.54 [− 0.136 to 0.873]). Expenses per capita were not correlated with GDP per capita (0.52 [− 0.15 to 0.87]).

Conclusions: In Hungary, Latvia, and Slovakia, a positive recommendation was associated with a reimbursement, and a negative one, with the lack of reimbursement. The reimbursement of oncology OD is associated with a growing burden for public budget, and the expenses are correlated with the total GDP. The highest share of drugs with any recommendation was observed in Poland, and the lowest, in Latvia and Romania. The share of reimbursed drugs was the lowest in Latvia and the highest in Poland.

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Keyword: Orphan drugs, Oncology, Reimbursement, Health technology assessment, Policy, Central and Eastern Europe

Background

Rare diseases mostly include inherited life-threatening or chronically debilitating diseases that affect fewer than 5 of 10,000 people, according to the definition developed by the European Medicines Agency (EMA). Oncological diseases constitute around one-third of rare diseases and include, for example, lymphoblastic leukaemia, CD30 + Hodgkin lymphoma, or advanced soft tissue sarcoma [1–5]. The reimbursement of those drugs—called oncology orphan drugs—is the main way of making them accessible for patients with rare oncological diseases.

The EMA approves orphan drugs through a centralised procedure and issues the orphan designation; however, the status for particular drugs varies between countries. Orphan drugs can be approved conditionally (if the required clinical data regarding, for example, safety and efficacy are not yet available but will become available within a specified period of time) or under exceptional circumstances (if the required data regarding, for example, safety will never be accessible, for example, due to ethical concerns) [6, 7].

Recommendations and the final reimbursement decisions made by health technology assessment (HTA) agencies in specific countries are particularly interesting for decision-makers in Central and Eastern Europe (CEE) because orphan drugs, in general, seem to be one of the most expensive pharmaceuticals [8]. It is becoming increasingly popular in CEE countries to implement special regulations regarding the reimbursement of orphan drugs, which affects not only the decision-making process but also the procedures of developing HTA recommendations and requirements [5]. The reimbursement of orphan drugs is the main determinant of patients' access to innovative therapies, with the better availability of treatments in western European countries, as shown by German and French research [5, 14]. However, no sub-analysis for oncology orphan drugs was performed in relation to the CEE countries which are characterised by limited access to orphan biotechnological drugs, with Macedonia and Estonia having only one drug reimbursed, followed by Romania and Serbia with two drugs reimbursed, Bulgaria with three drugs reimbursed, Slovakia with four drugs reimbursed, and Croatia with seven drugs reimbursed [16].

To fill the knowledge gap, we aimed to comprehensively review the process of developing the recommendations based on HTA practices in these countries as well as to assess and compare the percentage of HTA recommendations and reimbursement status for oncology orphan drugs in selected CEE countries. In addition, we aimed to assess an agreement between recommendations and reimbursement status within the CEE countries for all orphan drugs that were assessed in selected countries, as this would provide information on relations between HTA assessment and the final reimbursement decision. Finally, we aimed to evaluate the expenditures from the public budget on the reimbursement of oncology orphan drugs over the period of 3 years, from 2014 to 2016.

Results

We analysed 36 oncology drugs with orphan designation in 2017. Nine of them (25%) received conditional approval by the EMA and only 2 (5.56%) were approved under exceptional circumstances (Table 1).

Recommendations and reimbursement status

Of all analysed countries, the highest share of positive recommendations was observed for Bulgaria and Estonia and the lowest, for Latvia. Negative recommendations were issued only in Hungary, Latvia, Poland, and Slovakia. The remaining countries issued only positive recommendations or no recommendation at all, which was due to specific regulations in those countries (Table 2).

The share of reimbursed drugs ranged from 11.11% in Latvia to 41.67% in Poland, with an average value of 28.89% (Table 2).

Recommendations and reimbursement status in the context of the type of authorisation

The share of positive recommendations among conditionally approved drugs ranged from 0% in Czechia, Lithuania, and Slovakia to 22.22% in Bulgaria, Estonia, Hungary, and Poland. Considering exceptional circumstances, the share of positive recommendations ranged from 0% in Croatia, Estonia, Latvia, Lithuania, and Slovakia to 50% in Bulgaria, Czechia, Hungary, Poland, and Romania. Among drugs with no additional approval conditions, the lowest share of positive recommendations was observed in Latvia (12%), and the highest, in Estonia (44%) (Table 2).

Table 1 Reimbursement status and recommendations issued for analysed drugs in 2017

Medicine name	Active substance	Approval type	Recommendation/reimbursement In analysed countries									
			Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Adcetris	Brentuximab vedotin	Conditional approval	✓/✓	✓/✓	./✗	✓/✓	✓/✓	./✗	./✗	✓/✓	./✗	./✗
Arzerra	Ofatumumab	Unconditional	✓/✓	✓/✓	./✗	./✗	✗/✗	./✗	./✗	✗/✗	✓/✓	✓/✓
Atriance	Nelarabine	Exceptional circumstances	✓/✓	./✗	✓/✗	./✗	✓/✓	✗/✗	./✗	✓/✓	✓/✓	./✗
Blincyto	Blinatumomab	Conditional approval	./✗	./✗	./✗	./✗	✗/✗	./✗	./✗	✓/✗	./✗	./✗
Bosulif	Bosutinib	Conditional approval	✓/✓	./✓	./✗	✓/✓	✓/✓	✓/✓	./✗	✗/✓	✓/✓	./✗
Ceplene	Histamine dihydrochloride	Exceptional circumstances	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Cometriq	Cabozantinib	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	✗/✗	./✗	./✗
Dacogen	Decitabine	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	✓/✓	./✗
Darzalex	Daratumumab	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	✗/✗	./✗	✗/✗
Farydak	Panobinostat lactate anhydrous	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	✗/✗	./✗	./✗
Gazyvaro	Obinutuzumab	Unconditional	./✗	✓/✓	✓/✓	./✗	✓/✓	✓/✓	✓/✓	✓/✓	./✗	✓/✓
Gliolan	5-aminolevulinic acid hydrochloride	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Iclusig	Ponatinib	Unconditional	./✗	./✗	./✗	./✗	✗/✗	./✗	./✗	✓/✗	./✗	✓/✓
Imbruvica	Ibrutinib	Unconditional	✓/✓	./✗	./✗	✓/✓	✓/✓	./✗	✓/✓	✗/✓	./✗	✓/✓
Imnovid[a]	Pomalidomide	Unconditional	./✗	./✗	✓/✓	./✗	./✗	./✗	./✗	✗/✗	./✗	✗/✗
Kyprolis	Carfilzomib	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Lartruvo	Olaratumab	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Lenvima	Lenvatinib mesylate	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Lynparza	Olaparib	Unconditional	✓/✓	./✓	./✗	✓/✓	./✗	./✗	✓/✓	✗/✓	./✗	./✗
Mepact	Mifamurtide	Unconditional	./✗	./✗	✓/✓	✓/✓	✗/✗	./✗	./✗	✗/✗	./✗	✗/✗
Nexavar	Sorafenib	Unconditional	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	./✗	✓/✓	✗/✓	./✗	✓/✓
Ninlaro	Ixazomib citrate	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Onivyde	Irinotecan hydrochloride trihydrate	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Revlimid	Lenalidomide	Unconditional	./✗	./✓	✓/✓	✓/✓	✓/✓	✗/✗	✓/✓	✓/✓	./✗	✓/✓
Sprycel	Dasatinib	Unconditional	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓
Tasigna	Nilotinib	Unconditional	✓/✓	✓/✗	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓	✓/✓
Tepadina	Thiotepa	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✓	./✗	./✗
Thalidomide Celgene[b]	Thalidomide	Unconditional	./✗	./✗	./✗	✓/✓	✓/✓	./✗	✓/✓	✗/✗	./✓	./✗
Torisel	Temsirolimus	Unconditional	✓/✓	✓/✗	✓/✓	./✗	✓/✓	✗/✗	./✗	✗/✓	./✗	✓/✓
Unituxin	Dinutuximab	Unconditional	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Venclyxto	Venetoclax	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗
Vidaza	Azacitidine	Unconditional	✓/✓	✓/✗	✓/✓	✓/✓	./✗	./✗	✓/✓	✓/✓	./✗	✓/✓
Votubia	Everolimus	Unconditional	✓/✓	✓/✗	./✗	✓/✓	./✗	./✗	✓/✓	✓/✓	✓/✓	./✗

Table 1 (continued)

Medicine name	Active substance	Approval type	Recommendation/reimbursement In analysed countries									
			Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Xaluprine[c]	6-mercaptopurine monohydrate	Unconditional	✓/✓	./✗	✓/✓	✓/✓	✓/✓	./✗	./✗	./✗	./✗	./✗
Yondelis	Trabectedin	Unconditional	./✗	✓/✗	./✗	./✗	✗/✗	✗/✗	./✗	✓/✓	✓/✓	./✗
Zalmoxis	Allogeneic T cells genetically modified	Conditional approval	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗	./✗

Scheme: recommendation/reimbursement

✓—positive; ✗—negative;.—not issued

[a] Previously pomalidomide celgene

[b] Previously thalidomide pharmion

[c] Mercaptopurine nova laboratories

Table 2 Share of positive recommendations and reimbursement decisions in analysed countries with respect to the type of approval

Country	Approval type	Recommendation			Reimbursement		Total
		Positive	Negative	No recommendation	Reimbursed	Not reimbursed	
Bulgaria	Conditional approval	2 (22.22%)	0 (0%)	7 (77.78%)	2 (22.22%)	7 (77.78%)	9
	Exceptional circumstances	1 (50%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	2
	Unconditional	10 (40%)	0 (0%)	15 (60%)	10 (40%)	15 (60%)	25
	Total	13 (36.11%)	0 (0%)	23 (63.89%)	13 (36.11%)	23 (63.89%)	36
Croatia	Conditional approval	1 (11.11%)	0 (0%)	8 (88.89%)	2 (22.22%)	7 (77.78%)	9
	Exceptional circumstances	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2
	Unconditional	9 (36%)	0 (0%)	16 (64%)	6 (24%)	19 (76%)	25
	Total	10 (27.78%)	0 (0%)	26 (72.22%)	8 (22.22%)	28 (77.78%)	36
Czechia	Conditional approval	0 (0%)	0 (0%)	9 (100%)	0 (0%)	9 (100%)	9
	Exceptional circumstances	1 (50%)	0 (0%)	1 (50%)	0 (0%)	2 (100%)	2
	Unconditional	10 (40%)	0 (0%)	15 (60%)	10 (40%)	15 (60%)	25
	Total	11 (30.56%)	0 (0%)	25 (69.44%)	10 (27.78%)	26 (72.22%)	36
Estonia	Conditional approval	2 (22.22%)	0 (0%)	7 (77.78%)	2 (22.22%)	7 (77.78%)	9
	Exceptional circumstances	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2
	Unconditional	11 (44%)	0 (0%)	14 (56%)	11 (44%)	14 (56%)	25
	Total	13 (36.11%)	0 (0%)	23 (63.89%)	13 (36.11%)	23 (63.89%)	36
Hungary	Conditional approval	2 (22.22%)	1 (11.11%)	6 (66.67%)	2 (22.22%)	7 (77.78%)	9
	Exceptional circumstances	1 (50%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	2
	Unconditional	9 (36%)	4 (16%)	12 (48%)	9 (36%)	16 (64%)	25
	Total	12 (33.33%)	5 (13.89%)	19 (52.78%)	12 (33.33%)	24 (66.67%)	36
Latvia	Conditional approval	1 (11.11%)	0 (0%)	8 (88.89%)	1 (11.11%)	8 (88.89%)	9
	Exceptional circumstances	0 (0%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)	2
	Unconditional	3 (12%)	3 (12%)	19 (76%)	3 (12%)	22 (88%)	25
	Total	4 (11.11%)	4 (11.11%)	28 (77.78%)	4 (11.11%)	32 (88.89%)	36
Lithuania	Conditional approval	0 (0%)	0 (0%)	9 (100%)	0 (0%)	9 (100%)	9
	Exceptional circumstances	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2
	Unconditional	10 (40%)	0 (0%)	15 (60%)	10 (40%)	15 (60%)	25
	Total	10 (27.78%)	0 (0%)	26 (72.22%)	10 (27.78%)	26 (72.22%)	36
Poland	Conditional approval	2 (22.22%)	3 (33.33%)	4 (44.44%)	2 (22.22%)	7 (77.78%)	9
	Exceptional circumstances	1 (50%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	2
	Unconditional	8 (32%)	9 (36%)	8 (32%)	12 (48%)	13 (52%)	25
	Total	11 (30.56%)	12 (33.33%)	13 (36.11%)	15 (41.67%)	21 (58.33%)	36
Romania	Conditional approval	1 (11.11%)	0 (0%)	8 (88.89%)	1 (11.11%)	8 (88.89%)	9
	Exceptional circumstances	1 (50%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	2
	Unconditional	6 (24%)	0 (0%)	19 (76%)	7 (28%)	18 (72%)	25
	Total	8 (22.22%)	0 (0%)	28 (77.78%)	9 (25%)	27 (75%)	36
Slovakia	Conditional approval	0 (0%)	1 (11.11%)	8 (88.89%)	0 (0%)	9 (100%)	9
	Exceptional circumstances	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2
	Unconditional	10 (40%)	2 (8%)	13 (52%)	10 (40%)	15 (60%)	25
	Total	10 (27.78%)	3 (8.33%)	23 (63.89%)	10 (27.78%)	26 (72.22%)	36

Unconditional means that neither conditional approval nor exceptional circumstances were granted

Agreement between recommendations and reimbursement status

In Hungary, of all 36 analysed drugs, 17 had both a recommendation and reimbursement decision issued. All drugs with a negative recommendation were not reimbursed and all drugs with a positive recommendation were reimbursed, resulting in perfect agreement with a kappa coefficient of 1 [95% CI 1–1]. A similar situation was observed in Latvia where of all 36 analysed drugs 8 had both a recommendation and reimbursement status available. All 4 drugs with a negative recommendation received no reimbursement, and 4 drugs with a positive recommendation received reimbursement, resulting in perfect agreement with a kappa coefficient of 1 [95% CI 1–1]. Slovakia demonstrated perfect agreement (kappa coefficient of 1; 95% CI 1–1) due to all 10 drugs with a positive recommendation being reimbursed and all 3 drugs with a negative recommendation not being reimbursed. However, it was different in Poland where 23 out of 36 drugs were analysed and the kappa coefficient was 0.4 [95% CI 0.04–0.76]. This is because out of 11 drugs with a positive recommendation 2 did not receive reimbursement, and out of 12 drugs with a negative recommendation, 5 were finally reimbursed.

For the purpose of the additional analysis (i.e. sensitivity analysis), the lack of HTA recommendation was treated as the third category (in addition to positive and negative recommendations), which allowed for the calculation of weighted kappa coefficients for all countries, with the same set of drugs analysed in each country. The sensitivity analysis revealed that the agreement was 0.42 [95% CI 0.33–0.53] for Bulgaria, 0.14 [95% CI 0.02–0.27] for Croatia, 0.35 [95% CI 0.23–0.47] for Czechia, 0.42 [95% CI 0.31–0.53] for Estonia, 0.46 [95% CI 0.33–0.58] for Hungary, 0.20 [95% CI 0.05–0.35] for Latvia, 0.36 [95% CI 0.24–0.48] for Lithuania, 0.30 [95% CI 0.13–0.46] for Poland, 0.29 [95% CI 0.16–0.42] for Romania and 0.39 [95% CI 0.26–0.51] for Slovakia.

Public payer expenses for reimbursement of analysed orphan drugs

Total expenditures from the public budget on the reimbursement of oncology orphan drugs varied between countries and years. The expenditures ranged from almost 850 thousand euro in 2014 in Latvia to almost 75 million euro in 2016 in Poland. In all analysed countries, total expenses increased from 10% in Estonia to 243% in Lithuania between the years 2014 and 2016, with an average increase of 68%, as compared with an increase of only 8.5% in GDP and 9.3% in GDP per capita (Table 3).

Total expenditures on the reimbursement of analysed drugs were highly correlated with the total GDP in all countries, with a Pearson's correlation coefficient of 0.961 [95% CI 0.838–0.99] in 2014, 0.96 [95% CI 0.836–0.99] in 2015, 0.93 [95% CI 0.72–0.98] in 2016, and an average coefficient of 0.95 [95% CI 0.81–0.99]. All correlations were significant, with p-values of less than 0.0001 (Fig. 1).

Table 3 Total expenditures from public budget on the reimbursement of oncology orphan drugs

Country	2014 (million euro)	2015 (million euro)	2016 (million euro)
Bulgaria	11	13	16
Croatia	9	11	15
Czechia	27	36	44
Estonia	4	5	5
Hungary	18	27	41
Latvia	1	1	1
Lithuania	2	3	4
Poland	57	67	75
Romania	24	27	31
Slovakia	23	27	33

No significant correlations were observed for GDP per capita (Pearson's correlation coefficient: − 0.07 [95% CI − 0.67 to 0.59] in 2014, − 0.01 [95% CI − 0.64 to 0.62] in 2015, − 0.06 [95% CI − 0.66 to 0.59] in 2016, and an average of − 0.04 [95% CI − 0.66 to 0.6]) (Fig. 2). Moderate, non-significant correlations were observed between GDP per capita and total expenditures per capita with values of 0.5048 [95% CI − 0.1830 to 0.8608; $p = 0.14$) in 2014, 0.5427 [95% CI − 0.1320 to 0.8738; $p = 0.11$) in 2015, 0.4923 [95% CI − 0.1991 to 0.8564; $p = 0.15$) in 2016, and an average coefficient of 0.5206 [95% CI − 0.1522 to 0.8663; $p = 0.12$) (Fig. 3). Moreover, no significant correlations were observed when analysing the share of reimbursed drugs (Pearson's correlation coefficient: 0.536 [95% CI − 0.141 to 0.872] in 2014, 0.54 [95% CI − 0.136 to 0.873] in 2015, 0.536 [95% CI − 0.141 to 0.872] in 2016, and an average of 0.54 [95% CI − 0.136 to 0.873]). No correlation between GDP and the share of reimbursed orphan drugs was observed for analysed countries [12].

Recommendations and HTA policy in analysed countries

In Bulgaria, during the time of the observation, recommendations on the reimbursement of a specific orphan drug are issued by the HTA Commission, the situation was then updated and now the National council of pricing and reimbursement is performing the procedure for HTA evaluation, pricing and inclusion in to the PDL. A positive recommendation from the

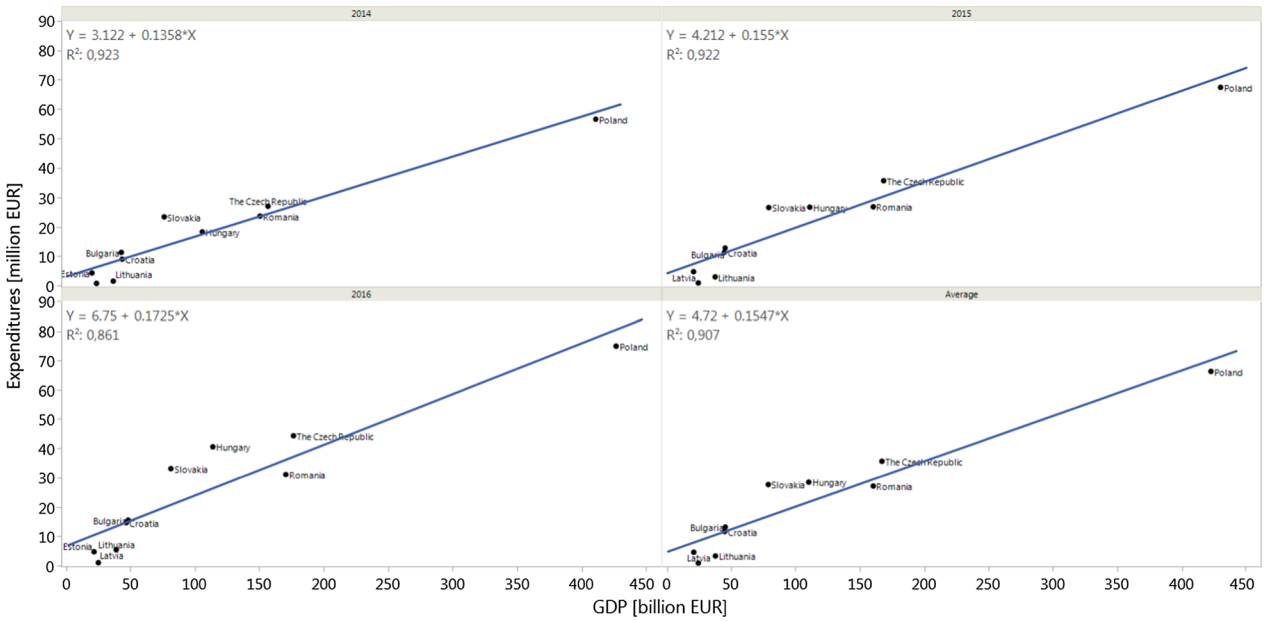

Fig. 1 Correlation between total gross domestic product (GDP) and total public expenditures on the reimbursement of analysed drugs in 2014, 2015, and 2016, as well as an average value

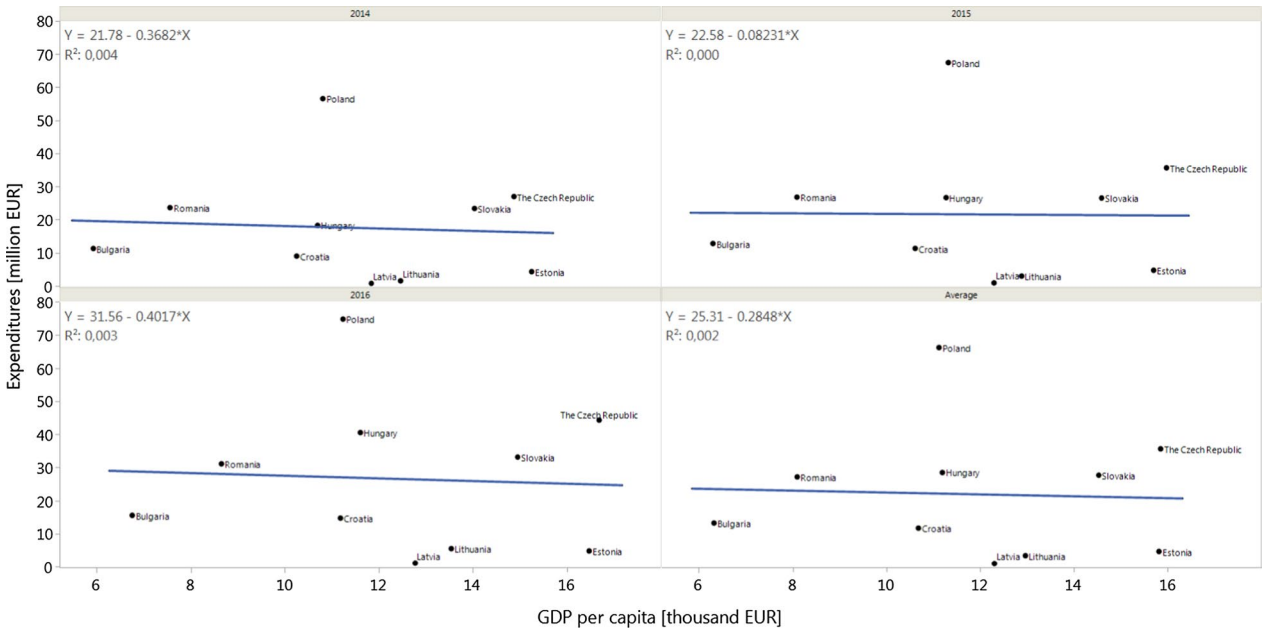

Fig. 2 Correlation between total gross domestic product per capita (GDP per capita) and total public expenditures on the reimbursement of analysed drugs in 2014, 2015, and 2016, as well as an average value

commission is one of the conditions for reimbursement. The final decision on reimbursement and inclusion in the Positive Drug List is made by the National Council for Prices and Reimbursement of Medicinal Products. Another obligatory condition is to sign a managed entry agreement with the payer. Only the positive reports of the commission are published (on the website of the National Centre of Public Health and Analyses, along with full HTA reports). Orphan drugs to be reimbursed do not necessarily need to show cost-effectiveness, the additional

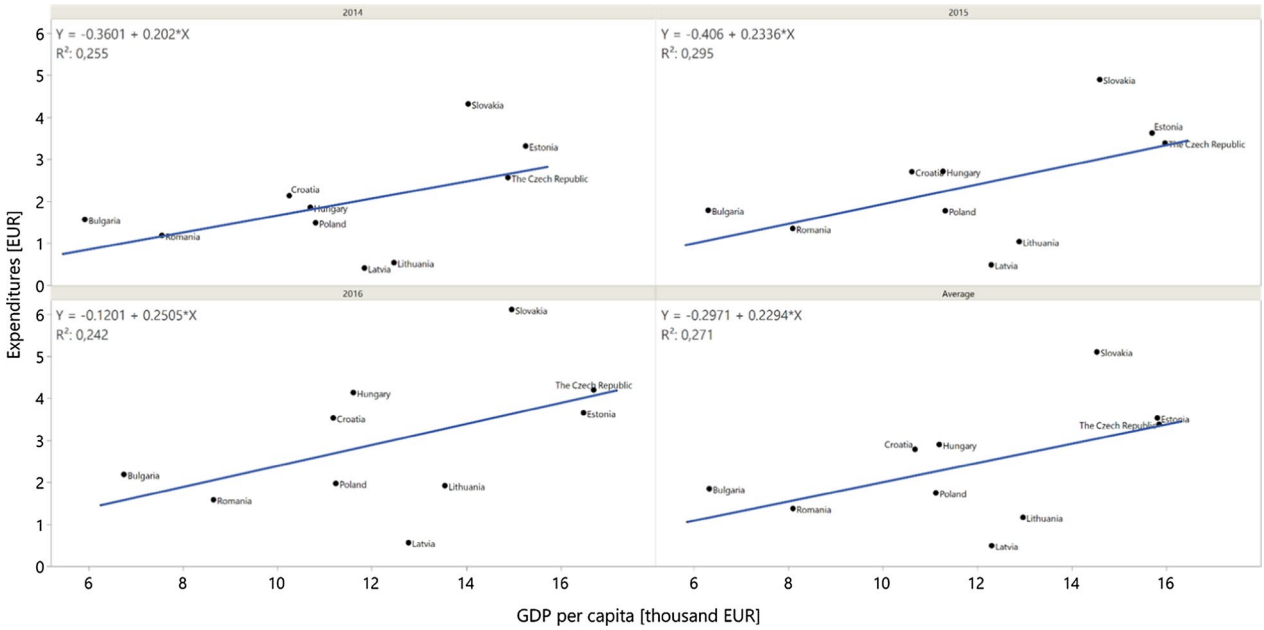

Fig. 3 Correlation between total gross domestic product per capita (GDP per capita) and total public expenditures on the reimbursement of analysed drugs per capita in 2014, 2015, and 2016, as well as an average value

assessments are also considered. HTA requirements include the results from clinical, pharmacoeconomic, and budget impact analyses, as well as ethical considerations. There is no need for an additional analysis. Bulgarian regulation on HTA necessitate for the applying products not to have negative HTA evaluation in UK, or France, or Germany. However nowadays it has changed and it is necessitate to have positive evaluation in UK, or France, or Germany, or Sweden (Table 4).

In Croatia, most of the recommendations for orphan drugs are solved by the Croatian Health Insurance Fund (CHIF)'s Committee for Medicines, but HTA Agency can make a recommendation on the reimbursement of a specific orphan drug on special request. A positive recommendation of the CHIF's Committee for Medicines means that the orphan drug will definitely obtain reimbursement. The CHIF's list of the reimbursed drugs is publicly available, but it does not explain the procedure itself. The recommendations for reimbursement are internal documents of the CHIF. HTA requirements include results from sensitivity analysis, modelling, subgroup analysis, and others (Table 4).

In Czechia, the State Institute for Drug Control (SUKL) acts as an advisory and a decision-making body. The recommendations are published on the website, along with administrative files that can be accessed only with an electronic signature. All recommendations and files are available only in Czech. In most situations, orphan drugs must show cost-effectiveness in order to be reimbursed, apart from highly innovative medicinal products. In general, the same reimbursement rules apply to both orphan and non-orphan drugs and include acceptable efficacy, safety profile, and HTA requirements (Table 4).

In Estonia, there is no separate HTA advisory body; however, in some situations, the Ministry of Social Affairs and Estonian Health Insurance Fund ask the University of Tartu for advice, as it has a working group that writes HTA reports on special request. The reimbursement decision depends primarily on the budget impact, and a positive recommendation by the University of Tartu (if requested) does not guarantee reimbursement. The recommendations are published quarterly at the website of the Ministry of Social Affairs, or once a year at the website of the Health Insurance Fund for health care services. The HTA requirements for orphan drugs are the same as for other drugs (Table 4).

In Hungary, several advisory bodies make HTA recommendations, including the National Institute of Health Insurance Fund Management, Department of Health Technology Assessment, HTA Committee, Ministry of Human Capacities, and National Pharmaceutical Therapeutic Committee. A positive recommendation by any of those bodies does not always translate into a positive reimbursement decision, because the reimbursement process is more complex. For new active substances or a new indication, it is necessary to amend the reimbursement law. Only the final decisions, but not recommendations, are published.

Table 4 Summary of aspects related to health technology assessment (HTA)

Question	Bulgaria	Croatia	Czechia	Estonia	Hungary	Latvia	Lithuania	Poland	Romania	Slovakia
Are there any advisory bodies (e.g. HTA agencies) that make recommendations whether or not to reimburse a specific orphan drug?	Yes	Yes	Yes	No	Yes	Yes	N/A	Yes	Yes	Yes
Does a positive recommendation mean the orphan drug will definitely be reimbursed?	No	Yes	Yes	No	No	No	Yes	No	Yes	No
Are the reimbursement recommendations publicly available?	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Does the orphan drug need to show cost-effectiveness to be reimbursed?	No	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	No	Yes
Does the orphan drug need to show an acceptable safety profile to be reimbursed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Does the orphan drug need to show acceptable efficacy to be reimbursed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Are there any HTA requirements for orphan drugs to be reimbursed?	Yes	Yes	Yes	Yes	Yes	No	N/A	Yes	N/A	Yes

*Not required for ultra-rare diseases; N/A – not applicable

The most important criteria for reimbursement are cost-effectiveness, equity, budget impact, the severity of illness, and efficacy. The acceptable safety profile is analysed before the marketing authorisation by the EMA or the National Institute of Pharmacy and Nutrition. The evaluation by an HTA department includes the analysis of the safety profile (e.g. considering real-world evidence, among other important factors). There are no separate HTA requirements for orphan drugs (Table 4).

In Latvia, decisions on reimbursement are made by the National Health Service (NHS). Internal National Health Service bodies make recommendations, which are published on the website. Inclusion in a positive drug list is possible if the drug is cost-effective, has no budget impact, or if additional financial resources are allocated for this aim (Table 4).

In Lithuania, there is no stand alone HTA body. However, therapeutic value of medicines applied for reimbursement is assessed by State Medicines Control Agency, whereas economic evaluation is carried out by the Pharmaceutical department of the Ministry of Health. Decision on reimbursement takes Reimbursement Commission of the Ministry of Health taking into account therapeutic and economical evaluation. Assessment reports of therapeutic value and economical evaluation as well as protocols of the meetings of the reimbursement commission are publicly available on the website of the Ministry of Health (in Lithuanian language). Drugs are reimbursed if they are included in the reimbursement list. Each drug to be included in a positive drug list must show cost-effectiveness, except for orphan drugs for ultra-rare diseases. Conditional approval or approval under exceptional circumstances are not specifically taken into account. Decision is made on evidence of clinical value (Table 4).

In Poland, there are 2 advisory bodies: the Agency for Health Technology Assessment and Tariff System (AOTMiT) and within AOTMiT the Transparency Council. The AOTMiT makes positive or negative recommendations. The Transparency Council issues opinions to the President of the AOTMiT that can also be positive or negative. Neither positive recommendation by AOTMiT nor TC guarantees reimbursement. All recommendations and opinions are publicly available at the AOTMiT's website (Table 4).

In Romania, the National Agency for Medicines and Medical Devices is an advisory body in the reimbursement decision-making process. A drug is reimbursed following the positive advice of the agency; however, new drugs that require additional funding are subject to volume price negotiations. Orphan drugs that are included in a national therapeutic programme are fully reimbursed. Once a drug receives a positive recommendation, it must be officially included in the list and the publicly available guideline for a specified disease is modified. Then, the drug is reimbursed by the Ministry of Health and National Agency for Medicines and Medical Devices (NHIH) (Table 4).

The Slovak Ministry of Health established the Reimbursement (or Categorisation) Committee to act as its advisory body with regards to reimbursement. The committee is supported by different advisory working groups, a medical board (assessing the effectiveness, safety, and importance of the medicine), and the Working Group for Pharmacoeconomics, Clinical Outcomes and Health Technology Assessment of the Ministry of Health. The recommendation of the Categorisation Committee can be overruled by the Minister of Health. Recommendations are publicly available at the website of the ministry. Orphan drugs must show cost-effectiveness; however, the thresholds were not applicable for orphan drugs indicated in the therapy of rare diseases with a prevalence of less than 1:100,000 in Slovakia. Based on the evaluation of the drug's effectiveness, safety, and importance as well as economic benefits, the Categorisation Committee determines its therapeutic and social value. Again, the thresholds were not applicable for orphan drugs indicated in the therapy of rare diseases with a prevalence of less than 1:100,000. The threshold prevalence was updated in 2018 to 1:50,000 (Table 4).

Discussion

The study revealed that most analysed countries implemented some sort of an HTA process in their reimbursement decision-making process and in the majority of these countries, publicly available reimbursement recommendations were used.

In general, in all analysed countries orphan drugs are required to be cost-effective, present an acceptable safety profile and high enough efficacy however different rules are applied when making final decision. Although the recommendations do not easily translate into positive reimbursement decision the observed kappa coefficients were high. The study showed that, in most countries, HTA recommendations are issued together with positive reimbursement decisions, which translates into a perfect agreement of 1. The exception was Poland, where the kappa coefficient was 0.4, mainly because almost 42% of drugs with a negative recommendation were finally reimbursed. Importantly, once the reimbursement recommendation is issued by the AOTMiT in Poland, the Marketing Authorisation Holder can enter negotiations with the Ministry of Health. This often results in reducing the cost of the drugs or introducing risk-sharing schemes, which has a direct impact on reimbursement. Unlike the

recommendations by the AOTMiT, the negotiations are not publicly available and thus cannot be analysed.

In addition, we assessed the burden of costs generated by the reimbursement of the analysed oncology drugs in the years 2014–2016 on the public payer budget. An average increase in public expenditures on the reimbursement was 68%, as compared with an increase of only 8.5% in the total GDP and of 9.3% in GDP per capita. The factors influencing the increase could be associated with an increased number of reimbursed drugs, subject that was covered extensively by Vokinger and Kesselheim [11] as well as changes in public budget expenditures or in reimbursement policy. Changes in pricing could also result in fluctuations in expenditures. In most cases, after the initial approval of the drug, some new clinical data regarding drug efficacy would emerge and could influence reimbursement decisions. Although the Committee of Human Medicinal Products does not have any direct influence on prising policy in European Union (EU) member states, the type of approval could be considered in the decision-making process [5]. Additionally, in this study, we focused on the analysis of growing expenditures in relation to growing GDP without considering the effect of various factors on the expenditures to reveal the burden of oncology orphan drugs on the public budget. Public expenditures were significantly correlated with the total GDP but not with GDP per capita or the share of reimbursed oncology orphan drugs, which might indicate that the reimbursement of oncology orphan drugs could be associated with the general size of country economics rather than the welfare of its citizens. This could result from a policy that is implemented by many countries, namely, to reduce expenses on public health to the country's GDP and not GDP per capita. The most informative correlation between GDP per capita and expenditures per capita was moderate in size, however statically insignificant.

To our knowledge, this is the first study to summarise HTA decision making regarding oncology orphan drugs in EU countries from the CEE region, as well as to analyse the dynamics of public expenditures on the reimbursement of those drugs in relation to the GDP and GDP per capita.

We were not able to collect relevant data for Slovenia, which is a limitation of the study. In addition, we used the kappa coefficient to analyse the agreement between recommendations and reimbursement status. However, the kappa coefficient of agreement could be calculated only for the countries that issued both positive and negative recommendations to provide some insight into the functioning of the reimbursement policy based on HTA-assessed drugs. Moreover, the coefficient might have been affected by the levels of analysed variables, and thus it can be treated as a descriptive rather than inferential statistics. As in other statistical tests, only cases (drugs) with both the recommendation and reimbursement status available were analysed, which resulted in different sets of drugs used to calculate kappa coefficients in different countries, this approach is however appropriate as using in analysis drugs that were not even considered for heath technology assessment could introduce bias into the analysis. Also, we observed that most kappa coefficients in this study were equal to 1. This could result from the fact that the countries significantly differed in terms of HTA processes, which translates into a considerable discrepancy in the shares of positive and negative recommendations. In some countries, advisory bodies issued only positive recommendations.

Another limitation is that the study focused on a set of oncology orphan drugs only in one year. Further research is needed to compare oncology orphan drugs to non-oncology ones (e.g. metabolic) and to analyse costs over a longer period.

In order to compare the results of our study, we reviewed medical databases to identify other important publications on this subject. Our previous study [5] analysed the status of all drugs with orphan designation and their relation to the type of EMA approval. In addition, we showed a significant variation in agreement with the reimbursement status of analysed drugs across selected European countries. The same list of orphan drugs was used in another study [12] that described the status of orphan drugs in CEE-EU countries. The reimbursement of orphan drugs was assessed without describing detailed HTA or public budget issues. Both studies showed a significant impact of the type of approval and disease on the reimbursement decisions. Moreover, they revealed that the shares of reimbursed orphan drugs are much higher in Western European than CEE-EU countries. In addition, we showed that the type of the disease was significantly associated with the type of marketing authorisation. We also reported that oncology drugs were significantly associated with the chances of reimbursement. For example, in Croatia, oncological orphan drugs were more than 5 times more likely to be reimbursed compared with non-oncology drugs (OR 5.33; 95% CI 1.31–21.68).

The field of oncology orphan drugs was examined in a research by Jarosławski et al. and revealed cost differences between oncology orphan drugs targeted at smaller populations and those targeted at larger populations in the United States [13]. No similar research was conducted for Europe. On the other hand Vassel et al. analysed whether children and adolescents with cancer benefited from the Orphan Drug Regulation in the EU

and showed that only 2% of oncology orphan drugs were designed for use by children. The analysis covered the period from 8 August 2000 to 10 September 2016 [15].

The subject of oncology orphan drugs is not yet well described, especially among CEE countries, which struggle with a growing burden of reimbursement for the public budget and which need detailed data for efficient reimbursement decision making and HTA assessment regarding orphan drugs (particularly those for oncological diseases).

Conclusions

In Hungary, Latvia, and Slovakia, a positive recommendation was associated with a positive reimbursement decision, while a negative recommendation, with a lack of reimbursement. The reimbursement of oncology orphan drugs is associated with a growing burden for the public budget, with an average 3-year increase in expenses of 68%, as compared with an increase of only 8.5% in the total GDP and of 9.3% in GDP per capita among CEE countries. The total expenditures on the reimbursement of oncology orphan drugs varied among countries and were highly correlated with the total national GDP but not with GDP per capita. Expenditures per capita also were not significantly correlated with GDP per capita. The highest share of drugs with any recommendation was observed in Poland, and the lowest, in Latvia and Romania. The share of reimbursed drugs was the lowest in Latvia and the highest in Poland.

Methods

In a previous study [5] we reviewed the EMA website [1] and identified all drugs with orphan designation in 2017. We also collected data on the type of approval, disease, and reimbursement status [4] for Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia. For the current study, we selected only drugs used in the treatment of oncological diseases (38% of all analysed drugs) and performed a questionnaire survey among experts from respective countries. We collected additional data on total public expenditures on the reimbursement of those drugs as well as HTA recommendations issued for those drugs by reimbursement advisory bodies operating in the analysed countries. As the economic burden generated for national public payers reflects real cash flows in the years 2014 to 2016, no inflation corrections were made. Local currency units were converted to euros. The total expenditures per year per drug per country included the cost of reimbursement, expenditures for individual request, and expenditures of partial reimbursement of specific drugs with patients' co-payment. The costs were presented from the perspective of health care system; no distinction was made on whether the cost of drug was totally covered by the public payer or was a patients' co-payment involved. Only budget impact was analysed which took into account real cash flows from the public payer hence the data has been already corrected for any existing risk sharing agreements or drug price differences [12]. The correlation between the total cost (as well as per capita) and gross domestic product (GDP) and GDP per capita was analysed using Pearson's correlation coefficient. Data on GDP in US dollars for each analysed year were derived from the World Bank [9] and were converted in euro using the following exchange rates: 0.7536 in 2014, 0.9017 in 2015, and 0.9042 in 2016.

Nominal variables were presented as counts and percentages. Cost data were rounded to units in euros. The agreement between a reimbursement recommendation and status in the CEE countries was assessed using the κ coefficient [10]. All κ coefficients were supported with 95% confidence intervals (CIs) and rounded to 2 decimal places.

Statistical analyses were performed in the JMP® software, version 14.2.0 (SAS Institute Inc., 2018, Cary, North Carolina, USA).

Abbreviations

HTA: Health technology assessment; EMA: European Medicines Agency; GDP: Gross domestic product; CEE: Central and Eastern Europe; CI: Confidence interval; CHIF: Croatian Health Insurance Fund; NHIH: National Agency for Medicines and Medical Devices; AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; SUKL: State Institute for Drug Control; NHS: National Health Service; TC: Transparency Council.

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Authors' contributions

KM performed the data synthesis and analysis as well as drafted the manuscript. PK designed and supervised the study, and wrote the final manuscript. WT supervised the study and critically reviewed the manuscript. CS contributed to review the manuscript and wrote the final version of the manuscript. GP, MM, AS, PD, JS, AM, KM, ZR, JG, TT, and MP provided necessary data and wrote country-specific sections of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Urzędów, 03.11.2020
(miejscowość, data)

dr. hab. Paweł Kawalec prof. UJ
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
koncepcja i projekt pracy, opracowanie metodologii i krytyczna korekta opracowania.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez Krzysztofa Malinowskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych. Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład Krzysztofa Malinowskiego przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Kawalec Paweł
(podpis wnioskodawcy)

Kraków, 03.11.2020
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Dr hab. Wojciech Trąbka
(tytuł zawodowy, imię i nazwisko)

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Wojciech Trąbka
(podpis wnioskodawcy)

Wien 4.11.2020
(miejscowość, data)

dr hab. Christoph Sowada
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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(podpis wnioskodawcy)

Bulgaria, Sofia, 3.11.2020
(place/city, date)

Guenka Petrova, PhD, DSCi
(degree, name and surname)

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

I hereby declare that my contribution involved participation in collecting data and preparing county-specific paragraph as well as proof-reading of the final version of the manuscript.

In addition I give my consent for Krzysztof Malinowski to use stated publication as part of his PhD dissertation in a form of collection of publications in scientific journals.

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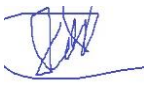

G. Petrova
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Sofia, 06.11.2020
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Prof. Manuela Manova, PhD
(degree, name and surname)

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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(signature)

Zagreb, 5. November 2020.

Associate Professor, MD; PhD, Pero Draganić

STATEMENT

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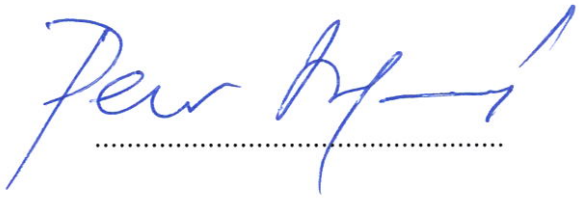

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Prague, 03.11.2020
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MUDr. Juraj Slabý
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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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A Männik
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KRISTOF MÁRKY
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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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Riga 03.11.2020.
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Zinta Rugaja
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As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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Vilnius, 04-11-2020

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Dr. Jolanta Gulbinovič

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(degree, name and surname)

STATEMENT

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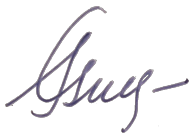

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Slovakia, Bratislava, November 03, 2020

Assoc. Prof. Tomas Tesar, PharmDr., PhD, MBA

STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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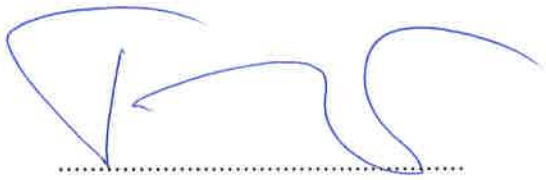

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Univ. Titu Maiorescu

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(place/city, date)

Bucharest Romania

Asoc Prof dr. Sorin Paveliu

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STATEMENT

As a co-author of the following publication Malinowski KP, Kawalec P, Trąbka W, Sowada C, Petrova G, Manova M, Savova A, Draganić P, Slabý J, Männik A, Márky K, Rugaja Z, Gulbinovic J, Tesar T, Paveliu MS. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. Orphanet J Rare Dis. 2020 Oct 8;15(1):277. doi: 10.1186/s13023-020-01556-9

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Pavel

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Podsumowanie

Analiza sytuacji leków sierocych w wybranych krajach, tj. Belgii, Danii, Francji, Niemczech, Włoszech, Polsce, Hiszpanii, Szwecji, Holandii oraz Anglii, Szkocji i Walii wykazała, że odsetek refundowanych leków sierocych różni się pomiędzy krajami, przy czym najmniejszy odsetek został zaobserwowany w Polsce, a największy w Danii.

Ocena zgodności w podejmowani decyzji refundacyjnych oraz rekomendacji HTA dotyczących leków sierocych pokazała, że najwyższa zgodność w decyzjach refundacyjnych została zaobserwowana pomiędzy Włochami i Hiszpanią; w przypadku rekomendacji HTA najwyższą zgodność zaobserwowano w przypadku Anglii i Szkocji.

Badanie rodzajów autoryzacji wydawanych przez EMA w odniesieniu do leków sierocych pokazało, że autoryzacja warunkowa istotnie zmniejsza szanse danego leku na refundację we Francji, Hiszpanii i we Włoszech, natomiast autoryzacja przyznana na specjalnych zasadach miała podobny efekt tylko w Niemczech.

Ocena wpływu typu choroby leczonej danym lekiem sierocym wyjawiła, że leki wykorzystywane w terapii schorzeń metabolicznych miały znacznie większe szanse na autoryzację na zasadach specjalnych i znacznie mniejsze szanse na autoryzację warunkową, w porównaniu do leków stosowanych w terapii schorzeń innych niż metaboliczne i onkologiczne. W przypadku leków stosowanych w terapii schorzeń onkologicznych zaobserwowano dokładnie odwrotną zależność.

Dogłębna analiza procesu podejmowania decyzji refundacyjnych w krajach UE-CEE tj. Bułgarii, Chorwacji, Czechach, Estonii, Litwie, Łotwie, Polsce, Rumunii, Słowacji i na Węgrzech wyjawiła, że niektóre z analizowanych krajów wprowadziły już specjalne regulacje dotyczące refundacji leków sierocych; w niektórych krajach zastosowano inny (wyższy) punkt odcięcia dla Inkrementalnego Współczynnika Efektywności Kosztów (ICER). Niektóre kraje takie jak Litwa czy Rumunia czy wprowadziły formalnego procesu HTA.

Analiza sytuacji leków sierocych w rozważanych krajach wykazała, że odsetek refundowanych leków sierocych znacznie różni się pomiędzy krajami, jednakże nie był istotnie skorelowany zarówno z całkowitym Produktem Krajowym Brutto (PKB) jak i z PKB per capita.

Ocena zgodności w podejmowani decyzji refundacyjnych dotyczących leków sierocych w krajach UE-CEE pokazała, że najmniejsza zgodność została zaobserwowana pomiędzy Estonią i Łotwą, natomiast największa pomiędzy Estonią i Litwą.

Dodatkowo w Czechach, Słowacji i na Litwie leki sieroce autoryzowane przez EMA warunkowo miały istotnie mniejsze szanse na refundację w porównaniu do pozostałych leków sierocych, co więcej w przypadku Chorwacji, Estonii, Węgier i Litwy leki sieroce stosowane w terapii chorób onkologicznych miały istotnie większe szanse na refundację w porównaniu do pozostałych leków sierocych.

Ocena systemu formułowania rekomendacji HTA w krajach UE-CEE pokazała, że na Węgrzech, Liwie oraz Słowacji pozytywna rekomendacja wiązała się z pozytywną decyzją refundacyjną dotyczącą danego leku, natomiast negatywna rekomendacja z brakiem refundacji.

Analiza podgrupy leków sierocych stosowanych w terapii schorzeń onkologicznych wykazała, że największy odsetek leków, które zostały ocenione w procesie HTA został zaobserwowany w Polsce a najniższy na Łotwie i w Rumunii, co znajduje odzwierciedlenie w odsetku refundowanych leków z analizowanej grupy, który jest największy w Polsce a najmniejszy na Łotwie.

Analiza wydatków z budżetu państwa na refundację onkologicznych leków sierocych wyjawiła rosnące obciążenie dla płatnika publicznego związane z refundacją tych leków. W ciągu trzech analizowanych lat wzrost wydatków wyniósł 68% przy czym zanotowany wzrost PKB oraz PKB per capita wyniosły odpowiednio 8.5% oraz 9.3% dla całej grupy krajów UE-CEE. Wydatki na refundację onkologicznych leków sierocych znacznie różniły się pomiędzy krajami jednak nie były skorelowane z PKB per capita lecz z całkowitym PKB danego kraju.

Summary

The examination of orphan drugs in selected countries i.e., Belgium, Denmark, England, France, Germany, Italy, Poland, Scotland, Spain, Sweden, The Netherlands, and Wales revealed that the percentage of reimbursed orphan drugs varied among the countries from the lowest in Poland to the highest in Denmark.

Analysis of agreement in decision-making regarding reimbursement of orphan drugs and HTA recommendations among analysed countries revealed that the highest, substantial agreement in reimbursement decisions was observed between Italy and Spain, and the highest agreement in recommendations was observed between England and Scotland.

Study of the EMA-issued type of authorisation of analysed orphan drugs showed that the conditional approval significantly decreased the chance for reimbursement in France, Italy, and Spain; however the approval granted under the exceptional circumstances had similar impact only in Germany.

Analysis of impact of the type of the disease treated with the specific orphan drugs revealed that the drugs for metabolic diseases were more likely to be approved under exceptional circumstances, but had lesser odds for being conditionally approved when compared to other drugs for non-metabolic and non-oncologic diseases. The opposite was observed for drugs used in treatment of patients with oncologic diseases.

In-depth study of reimbursement decision-making process among EU-CEE countries i.e., Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, and Slovakia revealed that some of the considered countries already established separate regulations on reimbursement of orphan drugs; in case of some of these countries higher ICER values for orphans are used; in Lithuania and Romania, no formal HTA process was employed.

The examination of orphan drugs in selected countries showed that the share of reimbursed orphan drugs varied significantly across the countries, but it was not associated either with GDP or GDP per capita.

Analysis of agreement in decision-making regarding reimbursement of orphan drugs revealed that the lowest, slight agreement in reimbursement decisions was observed between Estonia and Latvia, and the highest, substantial agreement, between Estonia and Lithuania.

Additionally, in Czechia, Lithuania and Slovakia, EMA's conditional approval significantly decreased the chances for reimbursement. What is more, in Croatia, Estonia, Hungary, and Lithuania, drugs for oncological diseases had significantly greater chances for reimbursement.

Detailed analysis of HTA recommendation-making process revealed that in Hungary, Latvia, and Slovakia, a positive recommendation was associated with a positive reimbursement decision, while a negative recommendation, with a lack of reimbursement.

The study of subset of orphan drugs used in treatment of oncology diseases showed that the highest share of drugs with any recommendation was observed in Poland, and the lowest, in Latvia and Romania. The share of reimbursed drugs was the lowest in Latvia and the highest in Poland.

Analysis of public expenditures revealed that the reimbursement of oncology orphan drugs is associated with a growing burden for the public budget, with an average 3-year increase in expenses of 68%, as compared with an increase of only 8.5% in the total GDP and of 9.3% in GDP per capita among EU-CEE countries. The total expenditures on the reimbursement of oncology orphan drugs varied among countries and was highly correlated with the total national GDP but not with GDP per capita. Expenditures per capita also were not significantly correlated with GDP per capita.