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Patterns of alternative access: Unpacking the Slovak extraordinary drug reimbursement regime 2012-2016

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ABSTRACT

Many countries employ "alternative access schemes" (e.g. compassionate use, early access programs, off-label use) that seek to provide patients with access to drugs not included on a positive drug list. These schemes offer flexibility to policy-makers but often lack transparency and clear rules. This ambiguity allows for dynamic responses to weaknesses in the main drug approval and reimbursement systems, but also opportunistic use by the health professionals, industry or patients. Yet, most descriptions of these schemes focus on the *de jure* rather than the *de facto* situation, presenting a potentially misleading picture. We describe one such scheme in practice: the Slovak "extraordinary reimbursement regime" (ERR), using semi-structured interviews with 18 experts and a new dataset of ERR drugs. The ERR expanded rapidly, doubling between 2012 and 2016. It combined features of four reimbursement schemes: (1) a backdoor market access for expensive drugs; (2) a compassionate use scheme for investigational drugs combined with a "legacy drugs" scheme for older unlicensed drugs; (3) a disease-specific scheme for cancer and orphan drugs; and (4) a scheme for off-label and "off-indication" drugs. These four features reflect broader challenges facing the Slovak reimbursement system. We conclude that detailed study of the type, size and evolution over time of alternative access schemes can serve as indicators of health policy objectives neglected by standard reimbursement systems.

1. Introduction

Health policy-makers in most European countries have put in place sophisticated health technology assessment (HTA) and pricing and reimbursement (P&R) procedures for pharmaceuticals to achieve effective use of limited public resources. In principle, only high-quality drugs that do not pose an undue burden for public budgets are placed on positive drug lists (PDLs). In practice, however, many countries have recourse to "alternative access schemes" that seek to provide patients with access to drugs that are not available to them via the PDL [1]. The English Cancer Drugs Fund is perhaps the best known example of such a program, circumventing the existing HTA-based system [2], but it is far from the only one. Other examples common in Europe include individual patient funding requests [e.g. 3], early access programs [4], compassionate use [5], named-patient basis early access [4,6,7], and off-label use [8,9].

The rules for reimbursing drugs via alternative schemes are typically more lenient than the standard HTA and P&R processes (as with the Cancer Drugs Fund). Alternative schemes are also often less transparent, using *ad hoc* criteria and post-market data collection – the fact that France is lauded as an exception in formalizing its compassionate and off-label rules is telling [10]. As such, alternative access schemes present "grey zones" of reimbursement governance, with unclear consequences for patient access, equity and public budgets [1]. As drug prices continue to grow, as has been the case in the past with orphan drugs [11] or novel drugs for hepatitis C [12,13] and high cholesterol [14], we can expect alternative

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access schemes to become ever more important. However, the combination of ambiguity with scope for interpretation of terminology and powerful incentives, for patients, health professionals, and manufacturers, creates considerable scope for dynamic responses to weaknesses in the main approval and reimbursement systems, including potentially opportunistic ones, so that the schemes are extended to medicines and indications for which they were likely never intended. Yet, most descriptions of these schemes focus on the *de jure* rather than the *de facto* situation, presenting a potentially misleading picture.

In this paper, we unpack one case of alternative access in practice: the Slovak "extraordinary reimbursement regime" (ERR). The ERR permits statutory health insurance funds to grant reimbursement to individual patients for drugs that are not on the country's PDL, similar to individual funding requests in the UK [3]. Following a change of ministers in 2016, the ERR had become a focus of domestic policy and media attention. An audit showed that ERR spending for the country's three statutory health insurers had tripled from less than €10 million to almost €30 million between 2011 and 2015 [15]. The press and civil society organizations highlighted opacity in the ERR's operations and raised concerns about equity, pointing to patients with rare diseases whose applications were treated differently by individual statutory health insurance funds [16,17]. The ERR, in other words, was a black box, in stark contrast to the country's otherwise highly transparent and cost-conscious P&R policy [18].

We examine how the Slovak ERR worked in practice during the years of its steep growth in 2012–2016. In particular, we analyse what drugs were funded by the ERR and why, as well as how the scheme was governed. To the best of our knowledge, this is the first detailed study of the *de facto* operation of an alternative access scheme in a European country.

2. Drug reimbursement in Slovakia

Slovakia has a social health insurance system with three nationwide statutory health insurance funds: the state-owned General Health Insurance Fund (*Všeobecná zdravotná poist'ovňa*, VšZP) covers about 63 percent of the population, while the two privately owned funds, Trust (*Dôvera*) and Union, cover the remainder of the population – about 27 percent and 9 percent, respectively. Decisions on pricing and reimbursement rates, including co-payment, are taken nationally by the Minister of Health upon advice of the Categorization Committee, composed of representatives of the Ministry of Health, payers, and clinicians nominated by the Minister. The Committee is in turn advised by a working group of clinical experts and the "Expert Working Group for Pharmacoeconomics, Clinical Outcomes and Assessment of Health Technologies", both appointed by the Minister from nominations by professional societies. Payers have two representatives in the working group on pharmacoeconomics (one for VšZP and one for the privately owned funds, with another three members representing the Ministry of Health), which is a key player in the reimbursement process [19], as it must certify the drug's compliance with Law 363/2011, which sets out strict cost-effectiveness requirements. During the period under study (2012–2016), a drug could only be included on the PDL if its incremental cost-effectiveness ratio per quality-adjusted life year was lower than 24 times the average monthly wage (€20,592 in 2016), and could be conditionally reimbursed if under 35 times the average monthly wage (€30,030). The thresholds were not applicable to drugs for diseases with prevalence below 1:100,000 [20]. Inclusion of drugs on the PDL that exceeded the upper threshold was not possible.

Law 363/2011 gave payers the possibility to fully or partially reimburse drugs that were not registered or reimbursed in Slovakia or drugs that are on the PDL but whose use goes beyond their indication or prescription restrictions. This procedure became known in Slovakia as applying for extraordinary (or exceptional) reimbursement ("*na výnimku*", literally "as a matter of exception"), termed ERR in this paper. The law specified that the case needed to be justified, "notably" by the drug being the only option to improve the patient's health status, and the application needed to be submitted by the patient's health care provider. No other criteria for making decisions on ERR applications were spelled out.

A 2017 reimbursement reform, implemented as of 2018 [21], modified some of these rules. We briefly describe the reform in the discussion.

3. Data and methods

Based on a request addressed to the Slovak Ministry of Health, we obtained a dataset of drugs reimbursed via the ERR by VšZP between 2012 and 2016. The dataset contained brand names of drugs reimbursed via the regime, the corresponding anatomical therapeutic chemical (ATC) groups, and the number of patients, packages, and cost per year per drug. All price data were adjusted for inflation using the Slovakian annual average inflation rates between 2012 and 2016 and expressed in 2012 Euros [22].

We complemented this data with information from the European Medicines Agency (EMA) and the Slovak State Institute for Drug Control websites [23,24]. We verified each ERR drug's status on the Slovak PDL by comparing the annual list of ERR drugs with PDLs for January each year, available on the Ministry of Health website [25], using the Microsoft Excel fuzzy lookup add-in.

Similar data could not be obtained from the remaining two privately owned statutory insurers, Dôvera and Union. The rest of this paper focuses exclusively on VšZP ERR. While this necessarily limits the breadth of our findings, VšZP is the most important player in Slovak ERRs thanks to its dominance in terms of both the percentage of population it insures and share of ERR applications. According to one report, almost 90 percent of all successful ERR requests in Slovakia in 2012–2015 were granted by VšZP, 10 percent by Dôvera and around 1 percent by Union, despite Dôvera's and Union's proportionally larger market share [16]. VšZP also tended to reject slightly fewer applications, about 10 to 11 percent in 2011–2015, compared with Dôvera's and Union's use of their discretionary prerogative to reject 14 percent on average. The net effect is that VšZP consistently accounted for about 80–82 percent of all extraordinary reimbursement requests paid in Slovakia, while Dôvera's share fluctuated around 16–20 percent and Union's was marginal at 0.09 to 2 percent (see supplementary table 1).

The VšZP dataset has several limitations. First, it does not specify the reason for granting individual exceptions, such as a particular indication. Second, especially for drugs without an EMA or ŠÚKL marketing authorization date, we were not able to reliably determine their intellectual property status. Third, for drugs without EMA registration, we were unable to identify indications systematically. Together, these limitations make it difficult to analyse, for example, the ERR's priority disease and spending areas (for instance, new cancer drugs) using quantitative data. However, by combining the database findings with qualitative interview data in a mixed-methods approach we were able to draw additional conclusions.

OL conducted two rounds of semi-structured expert and elite interviews [26,27] with 18 actors knowledgeable about Slovak HTA and reimbursement decision-making. Our research was approved by the Ethics Committee at the Department of Sociology, University of Cambridge. The first round of interviews was conducted in Bratislava in December 2016 and January 2017, while the second round took place over the telephone (one over email) in February

2018. The first round focused on general aspects of the Slovak P&R and HTA processes. The second round was informed by the VšZP dataset and focused specifically on the ERR. To solicit informed responses, we shared with interviewees selected findings from the dataset. We obtained informed consent from all interviewees. We protect the interviewees' anonymity by assigning numbers (e.g. "I-20″) and broad interviewee categories (see supplementary table 2). All interviewee quotes were translated from Slovak.

We identified interviewees via purposive sampling based on publicly available documents and subsequent snowballing. Repeated interviewees were selected for their detailed knowledge of the ERR. In total, 48 potential interviewees were identified; 28 were prioritized and contacted; 5 refused (3 of whom suggested alternative interlocutors from their organization) and 5 did not respond. 6 were approached for a repeated interview (1 did not respond and 1 could not be reached). Refusals and non-responses were spread evenly across interviewees' institutional affiliations.

Interview data was analysed by OL using qualitative content analysis based on inductive codes [28]. Quantitative data was analysed by MC and OL. All data was discussed with PO, ZK, LK, and MMK. All researchers contributed to concept development, data interpretation, and writing. Elite interviews face potential risks of omission, misrepresentation or deception by the interviewees; this risk was partially mitigated by our use of mixed methods, so that information was systematically triangulated with data from other interviews and, where available, published documents [29].

4. Results

The VšZP ERR expanded rapidly during the 2012–2016 study period. Spending patterns correspond to four distinct reimbursement schemes: a backdoor market access for expensive drugs; a compassionate use scheme for investigational drugs combined with a "legacy drugs" scheme for older unlicensed drugs; a disease-specific scheme for cancer and orphan drugs; and a scheme for off-label and "off-indication" drugs.

4.1. Evolution in time: growth all around

The ERR grew both in terms of patients and expenditure (Table 1). Between 2012 and 2016, the number of patients receiving ERR drugs, as well as spending on the regime, increased noticeably. The number of ERR drugs grew steadily and average yearly spending per patient increased by 18 percent, with a peak in 2013. The average total yearly spending per drug grew by 37 percent, while the average number of patients per drug remained more or less constant over the years at around 10 patients.

Despite these increases, however, ERR spending remained a minor, if increasing, part of VšZP's overall pharmaceutical spending: 1.8 percent in 2012 and 4.4 percent in 2016. As one payer elucidated, "[the ERR] is an emergency solution. It doesn't have a huge budget impact, the problem is the absence of criteria to [approve or reject an application]" (I-14 payer). Interviewees described the regime's growth, rather than total cost, as the main cause for alarm: "It's an increasingly important problem" (I-3, consultant); "there is a consensus that the [ERR] is not working as it should" (I-4, civil society).

4.2. A parallel reimbursement system, or a "legacy drugs fund"?

Most interviewees were concerned that the ERR was being used as "backdoor market access" for drugs which did not fulfil Slovakia's 2011 strict cost-effectiveness criteria: "It has become a parallel reimbursement system" (I-22, civil society). Interviewees concurred that most new medicines were reimbursed only through the ERR, which they treat as a standard alternative: "Expensive medicines don't even apply for regular reimbursement. They're all pushed into the system through [the ERR]" (I-5, consultant). Conditional reimbursement was described as unattractive to manufacturers because of its low threshold as well as its long-term uncertainty.

Perhaps surprisingly, interviewees insisted that the ERR also included a number of old, cheap branded medicines or even generics that had been withdrawn for safety concerns or discontinued for business reasons (see Ref. [30]). They may not be obsolete from a clinical point of view, but rather not viable from a business perspective because of their low prices on the Slovak market, and thus unattractive to marketing authorization holders. These drugs, which we here call "legacy drugs", then need to be procured from abroad for individual patients. Legacy drugs do not have a valid marketing authorization with the Slovak ŠÚKL or the EMA. This would be similar to a compassionate use function, but for drugs not currently applying marketing authorization. The VšZP data does not allow us to conclusively confirm or disprove this assertion, but several conclusions can be reached by studying the relative importance of drugs grouped by their age for the cost of the ERR (see Fig. 1). In short, old and unregistered drugs constitute the majority of all ERR drugs, but their financial impact is relatively limited; new drugs are more limited in numbers but are responsible for most ERR spending.

Old drugs registered by the EMA before 2002 (10 years prior to the beginning of our dataset and the entry into force of Law 363/2011) made up about 9 percent of ERR drugs, and were responsible for about 9 percent of total spending throughout the five years. Drugs registered by ŠÚKL before 2002 made up about 15 percent of all ERR drugs but only about 8 percent of total spending. Drugs registered by both regulators made up 5 percent of ERR drugs and 7 percent of total cost.

Most numerous were drugs not registered by the EMA, ŠÚKL or either of the regulators, which made up 50 percent, 29 percent and 26 percent of all ERR drugs, respectively. These could be drugs in Phase III clinical trials, which would suggest the ERR is being used

Table 1
The evolution of Slovak VšZP extraordinary reimbursement regime.

	2012	2013	2014	2015	2016
Sum of number of patients	1,517	1,930	1,986	2,395	2,806
Sum of annual cost (EUR)	13,607,581	17,682,662	18,143,886	21,468,855	27,491,069
Number of drugs	166	180	197	229	245
Average number of patients per drug	9	11	10	10	11
Average total cost per drug (EUR)	81,973	98,237	92,101	93,750	112,208
Average cost/patient (EUR)	14,069	17,763	16,449	16,659	16,587
Total spending on drugs VšZP* (EUR)	749,823,041	601,360,210	621,115,496	636,003,306	666,308,265
Extraordinary reimbursement as percentage of total VšZP spending on drugs	1.81%	2.87%	2.87%	3.32%	4.14%

Source: authors, based on VšZP dataset. Note: VšZP = General Health Insurance Fund (*Všeobecná zdravotná poist'ovňa*).

* Source: Národné centrum zdravotníckych informácií (National Center for Health Information): Health Yearbooks 2012–2016, available at http://www.nczisk.sk/en/Publications/Edition_Health_Statistics_Yearbooks/Pages/default.aspx.

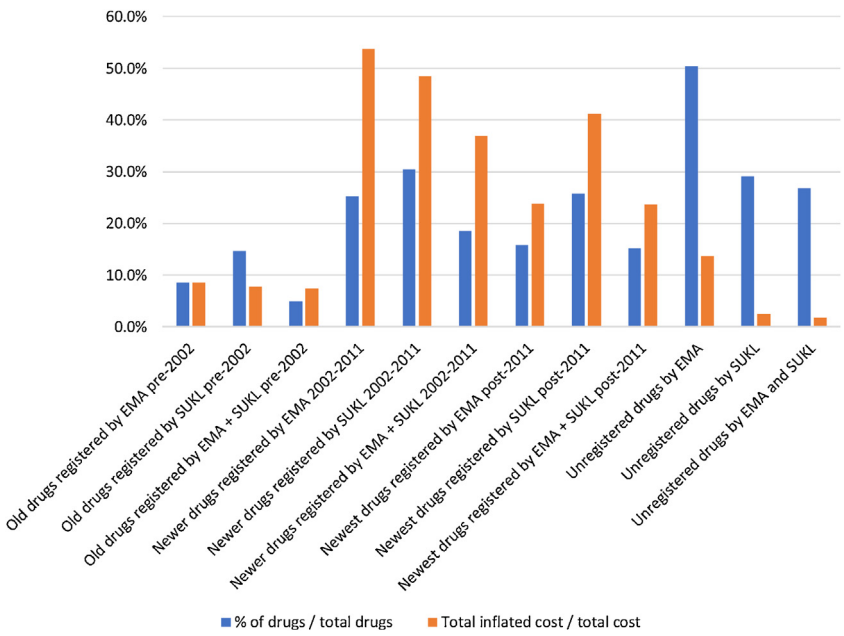

Fig. 1. Percentage of all ERR drugs and total 2012–2016 spending per drug registration date and regulator.
Note: due to overlaps between drugs registered (or not) by the EMA and by ŠÚKL, percentages add up to more than 100. EMA = European Medicines Agency; ŠÚKL = State Institute for Drug Control.
Source: authors, based on VšZP dataset.

for named-patient basis early access or compassionate use scheme for investigational drugs. However, it is more likely that they are in fact legacy drugs which had been introduced on the market before the EMA centralized procedure (for those with no EMA registration) and/or had their registration withdrawn in Slovakia (for those with no ŠÚKL registration). (Legacy drugs may be authorized in other EU member states and thus available via the mutual recognition procedure [31]). This is the scenario suggested by the spending pattern: drugs registered by ŠÚKL but not EMA were responsible for about 15 percent of total spending in 2012, a figure that remained stable at 14 percent in 2016 (Supplementary figure 1). Given this relatively low expenditure, we can expect most of these drugs to be older, pre-dating the centralized European authorization procedure, or falling out of its scope, which covers drugs for high priority diseases and/or important innovations.

In terms of spending, though, by far the most important category were "newer" drugs registered between 2002 and 2011 by the EMA (responsible for 54 percent of total spending, and 25 percent of all ERR drugs), followed by those registered during 2002–2011 by ŠÚKL (49 percent of spending for 30 percent of drugs), and the "newest" drugs registered after 2011 by ŠÚKL (41 percent of spending for 26 percent of drugs) (Fig. 1). This is also visible in the temporal pattern with a steady annual increase both in the number of drugs registered after 2002 and 2011 (Supplementary figure 2) and in spending (Supplementary figure 3) throughout the years. Drugs registered with ŠÚKL after 2011 made up 24 percent of all ERR spending in 2012 and gradually increased to 57 percent by 2016. Spending on these drugs in 2016 was 4.8 times higher than in 2012 after adjusting for inflation. Drugs registered with the EMA after 2011 made up 2.6 percent of all ERR spending in 2012 and gradually increased to 44 percent by 2016 (we can reasonably expect the Slovak registration process to lag somewhat behind the EMA and thus to also include drugs registered by the EMA several years prior to 2011). Spending on these drugs in 2016 was almost 34 times higher than in 2012. In terms of the relative contribution of these different drug categories to the annual growth in ERR spending, drugs registered between 2002 and 2011 were responsible for most of the growth (range of the contribution to growth: 72–77 percent). Drugs registered by either of the regulators after 2011 and unregistered drugs contributed less to the ERR's growth, while old drugs, registered before 2002, became less important financially as ERR spending grew (see Supplementary table 3). While this does not in itself confirm the ERR as "parallel reimbursement" from the point of view of the manufacturers, it strongly suggests that the regime is used as an access route from a patient and provider perspective.

4.3. Priority disease areas: cancer and rare conditions

The effects of the rigid reimbursement threshold were seen by nearly all interviewees as a driver of the increase in ERR expenditure, particularly because of new oncology drugs. Two reports document manufacturers' reticence to apply for inclusion of cancer drugs on the PDL [32,33], which was a common cause of concern. As one interviewee commented, "The whole of oncology has been dead since 2011″ (I-7, patient).

The ERR was thus seen as the only route through which Slovak patients could gain access, notably, to new cancer treatments. A payer described patient access enabled by the ERR as satisfactory: "Drugs are available because they get to patients via the ERR. Patients get them in 70–80 percent of cases, and these are drugs which have problems getting listed even in rich countries" (I-6). Similarly, an industry representative estimated that "40–50 new drugs haven't been put on the PDL after 2011. Not all of them are available [through the ERR], but most are" (I-26).

Table 2 presents the 20 most expensive drugs in VšZP's ERR over the entire 2012-16 period. Altogether, they made up 58.5 percent of the total expenditure of the ERR. As for disease areas, 11 are cancer drugs; three target diseases of the nervous system, and a further three are enzyme replacement therapy for rare diseases. The 20 most expensive drugs were used to treat a total of maximum 2,574 patients over the years (a quarter of the 10,634 patients overall). Importantly, eight of these drugs are subject to additional monitoring as per their EMA registration, including two being subject to conditional approval and exceptional circumstances at approval,

Table 2
Overview of 20 most expensive drugs in VšZP ERR.

Name of drug (International non-proprietary name)	Total cost per 5 years (in EUR)	Patient numbers*	Orphan status	Year of registration EMA	Year of registration SK	ICD-10 category	EMA notes
REVLIMID (lenalidomide)	6,622,810	247	Y	2007	2013	Neoplasms	EMA monitoring
DUODOPA (levodopa/ carbidopa)	6,177,119	191	N	–	2005	Diseases of the nervous system	
SOLIRIS (eculizumab)	5,018,237	17	Y	2007	2007	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	
AVASTIN (bevacizumab)	4,039,462	320	N	2005	2005	Neoplasms	
ELAPRASE (idursulfase)	3,192,546	5	N	2007	2007	Endocrine, nutritional and metabolic diseases	EMA monitoring
ZAVESCA (miglustat)	3,163,609	27	Y	2002	2002	Disorders of sphingolipid metabolism	
ADCETRIS (brentuximab vedotin)	2,871,683	71	Y	2012	2012	Neoplasms	Conditional EMA approval, EMA monitoring
ZELBORAF (vemurafenib)	2,733,770	86	N	2012	2012	Neoplasms	
IMBRUVICA (ibrutinib)	2,483,885	69	Y	2014	2014	Neoplasms	EMA monitoring
ZYTIGA (abiraterone)	2,248,280	157	N	2011	2016	Neoplasms	
AFINITOR (everolimus)	2,153,459	143	N	2009	2012	Neoplasms	
JAKAVI (ruxolitinib)	2,055,720	92	Y	2012	2012	Neoplasms	
GILENYA (fingolimod)	2,047,554	184	N	2011	2011	Diseases of the nervous system	EMA monitoring
NAGLAZYME (galsulfase)	2,019,589	4	N	2006	2008	Endocrine, nutritional and metabolic diseases	EMA monitoring, Exceptional circumstances at approval
SPRYCEL (dasatinib)	2,002,354	86	Y	2006	2010	Neoplasms	
CEREZYME (imiglucerase)	1,974,316	11	N	1997	1997	Endocrine, nutritional and metabolic diseases	
XALKORI (crizotinib)	1,969,781	65	N	2012	2012	Neoplasms	EMA monitoring
LEVACT (bendamustine)	1,678,221	589	N		2011	Neoplasms	
HUMIRA (adalimumab)	1,588,260	156	N	2003	2015	Diseases of the musculoskeletal system and connective tissue	
KEYTRUDA (pembrolizumab)	1,487,838	54	N	2015	2015	Neoplasms	EMA monitoring
Total	57,528,493	2 574					

Source: authors, based on VšZP dataset. Note: VšZP = General Health Insurance Fund (*Všeobecná zdravotná poist'ovňa*).
*The total number of patients may be lower, due to some patients being potentially included in two or more years.

respectively, indicating the regulator's concerns about safety and efficacy.

In practice, the absolute availability of new therapies in Slovakia was perhaps less problematic than the lack of explicit indication criteria and restrictions on patient populations. Patient populations were determined by each payer: "We try to set restrictions together with experts, but it is never for the full population need" (I-14, payer). An industry representative noted: "The problem is that twenty patients get the drug instead of a hundred. [. . .] New drugs are available, but according to criteria mastered by no-one" (I-26). Interviewees pointed to disparities among patient groups: where expensive innovative therapies had been put on the PDL before 2011, serving later as comparators, patients had relatively high standards of care, for instance in rheumatology (I-7, patient). Cancer patients, on the other hand, had to rely on the ERR.

The same was the case for some patients with rare diseases. Although drugs for rare diseases were not legally required to prove their cost-effectiveness, the definition of a rare disease for reimbursement purposes by Law 363/2011 was more restrictive than requirements for European Union orphan designation (maximum prevalence 1 in 100,000 in Slovakia, compared to 5 in 10,000 for the EMA). This created a gap in access to orphan drugs (I-5, I-1), where, according to a consultancy report, most drugs with EMA orphan designations did not apply for the PDL [33]. Table 3 shows that the number of orphan drugs as well as patients in the ERR continually grew, including the average number of patients per drug (from 7 to

Table 3
Drugs with EMA orphan designation in VšZP extraordinary reimbursement regime.

	2012	2013	2014	2015	2016
Sum of number of patients	163	201	242	308	393
As percentage of total number of patients	10.7%	10.4%	12.2%	12.9%	14%
Sum of annual cost	3,961,565	5,498,522	6,911,543	8,834,770	11,013,738
Number of drugs	22	21	32	38	39
Percentage of total cost	29.1%	31.1%	38.1%	41.2%	40.1%
Average number of patients / drug	7	7	8	8	10
Average total cost	180,071	189,604	215,986	232,494	282,404
Average cost/patient	37,506	45,537	33,308	28,179	30,888

Source: authors, based on VšZP dataset.

10 over the years). Part of the growth may be due to an increased number of oncology drugs with EMA orphan designation in the ERR. Seven of the 20 most expensive drugs had orphan designation, out of which five are cancer drugs. Orphan drugs were responsible for about 29 percent of ERR spending in 2012; this share increased to 40 percent by 2016. We also observed a 2.8 fold increase in annual spending on orphan drugs. Orphan drugs were given for about 11 percent of the total patients in ERR in 2012, and this share remained relatively stable over time, reaching 14 percent by 2016.

4.4. Overlap with positive drug list: off-label or off-indication

A significant proportion of drugs were reimbursed via the ERR while simultaneously being on the PDL. While 51 percent of ERR drugs were not reimbursed through the ordinary PDL procedure in any given year, 31 percent of them were included on both lists for all five years of the study period, with the remainder being included on both lists for at least one year. The proportion of drugs on both lists increased steadily from 19.9 percent in 2012 to 27.7 percent in 2016 (supplementary table 4).

These drugs may, in principle, fall into three categories. First, they can be used "off-label", for treating an indication for which they had not been licensed by ŠÚKL or the EMA [5], a practice common globally [9,10]. Second, they can be "off-indication" according to the Slovak PDL. In this case, the relevant indication may well be on-label per EMA (and/or ŠÚKL) registration, but not included on the PDL, most often presumably because of exceeding the cost-effectiveness threshold for the given indication (but satisfying it for others). Third, these drugs can be "off-prescription restrictions", i.e. requested by physicians who are not authorized to prescribe them.

The VšZP data does not allow us to differentiate between these cases. Interviewees, however, saw the off-label and off-indication uses as most common, and the "off-prescription restrictions" situation as marginal. They also described off-label and off-indication uses as "completely legitimate" (I-7, patient): "These [are probably] experiments with fourth, sixth-line treatment. . . I understand that the clinician wants to try anything, this is fully *lege artis*" (I-3, consultant).

5. Discussion

This paper set out to unpack the Slovak extraordinary reimbursement regime in 2012–2016 as a case of alternative access schemes in a single jurisdiction. Our study has three major limitations. First, the quantitative part of our data relies on a single statutory payer, the VšZP. Second, our data did not include details of the indications of the funded ERR drugs, limiting our ability to interpret some findings. Third, our analysis is based on a single case study that is, to a certain extent, idiosyncratic. For example, while the Slovak "legacy drug scheme" may look familiar to small countries with low drug prices, its generalizability to jurisdictions seen as core pharmaceutical markets is likely limited.

We found that, rather than providing a coherent funding scheme for a defined group of patients or drugs, the ERR encompassed all cases left behind by ordinary reimbursement rules, resulting in an amalgam of various alternative access schemes. First, the ERR was used as a "backdoor market access" chiefly for new expensive drugs, circumventing Slovakia's strict P&R rules. Second, it served as a compassionate use scheme for unlicensed investigational drugs, as well as a "legacy drugs fund" for old drugs no longer authorized on the Slovak market. Third, and in financial terms most importantly, it acted as a disease-specific fund for cancer and orphan drugs, analogous to the English Cancer Drugs Fund [34]. Finally, the ERR overlapped with the positive drug list, indicative of off-label and "off-indication" use.

The type, size and evolution over time of alternative access schemes can serve as indicators of the ability of a health system to respond dynamically, even if to some extent informally, to perceived problems with standard reimbursement systems, that increasingly employ sophisticated "template driven" [35] methods based on evidence-based medicine and HTA. The Slovak ERR data did not allow us to establish the relative size of each of its components in terms of number of drugs or patients, or spending. Nonetheless, our observations point to several issues with Slovakia's P&R system. First, the dominance of cancer drugs in the Slovak ERR points to an underserved patient population. Second, the existence of the off-label/off-indication category indicates an evolving gap between clinical practice and regulatory or reimbursement restrictions, and by extension a possible disconnect between tolerance and interpretation of risk by experts as opposed to the patients or their physicians. Third, the ERR's expansion could suggest that the PDL was failing to meet the needs or demands of certain populations. However, it is also necessary to determine whether this demand reflects genuine unmet medical need or supplier-induced demand for certain products. Without transparent data on unmet patient need for different conditions and individual ERR requests in Slovakia, this is difficult to assess.

Reasons for the evolution of alternative access schemes are context-dependent. In Slovakia, ERR growth corresponded with the 2011 P&R reform. In addition to the strict cost-effectiveness threshold, the reform's exceptional degree of transparency [18] prevented payers from concluding confidential price agreements with manufacturers. In response, a 2017 reform (chiefly Law 336/2017) increased the lower and upper cost-effectiveness thresholds used in pharmacoeconomic analyses from 24 to 35 times the average monthly wage to 35–41 times (arriving at around €37,000 in 2018, above the National Institute of Health and Care Excellence threshold in England) and allowed for the consideration of multiple criteria in determining cost-effectiveness. Manufacturers of medicines with fewer than 1:50,000 eligible patients were exempted from submitting cost-effectiveness analysis prior to reimbursement decisions. In parallel, it introduced the possibility of confidential managed-entry agreements, and mandatory paybacks for drugs under volume-capped conditional reimbursement (for any drug, including "orphan" drugs, with budget impact above

€1.5 million per year). It also regulated the ERR: off-indication and unregistered drugs need approval from the Ministry of Health and may be reimbursed up to 100 percent. All other drugs may be reimbursed to a decreasing extent over time (90 percent of their price in the first year on the Slovak market, 80 percent in their second and 75 percent in their third year) and are subject to a 5 percent co-payment by the provider – the latter condition was scraped later in 2018 following widespread concerns about patient access [36]. Drugs rejected from the ordinary reimbursement scheme on cost-effectiveness grounds became exempt from the payment limits and provider co-payment, in order to incentivize manufacturers to apply via the ordinary reimbursement procedure. Experts have since questioned the economic rationale for the reform's increase of the cost-effectiveness threshold [37]. The Ministries of Finance and Health, in turn, criticized the reform for incentivizing manufacturers to artificially restrict indications in order to bypass cost-effectiveness requirements by claiming to have a "rare disease" target population of less than 1:50,000 [38]. The reform was further amended as of January 2019 [37].

Whether these changes will be successful in containing the ERR's growth remains to be seen. Broader structural factors are also likely at play here: namely, the surge of premium-priced drugs over the past decade; the popularity of international reference pricing in other jurisdictions (affecting manufacturers' willingness to enter a low-priced market); and the low priority that small markets receive from the original and generic industries. That these factors played a role in Slovakia is suggested by the similar or even stronger growth of equivalent programs in other countries, e.g. in Hungary and the Czech Republic [39], or other alternative schemes, e.g. in Scotland [40].

6. Conclusions

This paper looked into the "black box" of the alternative access scheme in Slovakia. Our case study shows that studying alternative access schemes can act as an indicator of the "health" of P&R policies by identifying the kind, size and importance of patient populations left behind by PDLs. Their analysis can help policy-makers decide whether and how to structure their response.

The existence of alternative schemes *per se* is not necessarily undesirable. They offer important flexibility to accommodate individual patients' needs, as well as specificities of some drugs or patient groups. As the Slovak case illustrates, however, they can present normative problems. One such issue is their lack of transparency and clear rules for including patients' views [41]. Although the ERR was used to improve equity between patient groups (with cancer and rare disease patients facing disadvantages on the PDL), the opacity of the regime and the lack of criteria for granting individual applications created concerns over equity within these groups, which are difficult to dissipate without further data. More transparency and greater research on alternative access schemes would help to clarify their role in contemporary pharmaceutical policies and practices.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2019.05.021.

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