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Access to orphan drugs – comparison across Balkan countries

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ABSTRACT

The aim of this study was to compare orphan drug access in a sample of Balkan countries: five EU Member States (Bulgaria, Croatia, Greece, Romania, Slovenia) and two EU Candidates (Serbia, Montenegro). The comparative analysis was based on a cross-sectional study and included medicinal products with an active orphan designation and market authorisation on January 1, 2017.

Access to orphan drugs is an ongoing challenge in these countries. Three clusters of countries were identified in terms of orphan drug access: Greece and Slovenia, making the top tier, Romania, Bulgaria, and Croatia, being in the middle, and EU Candidates, Serbia and Montenegro, forming the bottom tier, where a substantial number of EU market approved orphan drugs was not even registered. Available public health resources and market size are probably among the contributing factors for such inequalities. Sizeable part of EMA market authorised orphan medicinal products is not even priced in the Balkan countries. This is a serious issue, which is putting rare disease patients from this region in a particularly vulnerable situation.

There is a need for further improvement in accessibility of orphan drugs in the Balkan countries. Cross-border collaboration in the field of pricing, health technology assessment, and reimbursement negotiation of orphan drugs may help to address these challenges.

1. Introduction

Orphan drug legislation was enacted in the European Union (EU) 17 years ago [1]. Regulation 141/2000 defines orphan drugs as medicinal products (A) that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the EU, or that are intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product would generate sufficient return to justify the necessary investment; (B) and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition [1].

Effective access of rare disease patients to orphan drugs is a complex process, combining market approval at EU level and reimbursement decision-making at national level. Market availability of orphan medicinal therapies is largely considered as a policy success. By February 2017, there are about 1450 positive opinions on orphan designations for a variety of active substances for different rare disease indications [2]. During the same period, nearly 130 orphan drugs have been granted marketing approval by the European Medicines Agency (EMA) [2]. On the other side, access to orphan drugs at national level remains a persisting problem. Due to the high costs of these therapies, reimbursement is the only viable option for effective patient access [3,4]. Significant variability and inequality in the number of accessible orphan drugs have been reported for different EU Member States [5,6]. A recent study from 2015 demonstrated that only 21.2% of 101 market approved orphan drugs were reimbursed in a selected sample of countries (Germany, France, the Netherlands, Poland, Sweden, England, Scotland and Wales) [7].

Accessibility of orphan drugs in Eastern Europe and especially the Balkan region, which includes both EU Member States and Candidates, is even more problematic. EU centralised market authorisation of orphan drugs is not valid in non-Member States [8–10]. The majority of these countries are small pharmaceutical markets with little power in pricing and reimbursement negotiations. Last but not least, health resources of Balkan countries are considerably limited, making the budget impact of these expensive

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Table 1
Methodological framework of the study.

Analytical tool	3-step process of access to orphan drugs		
	(1) Market authorisation	(2) Pricing	(3) Reimbursement
Definition of access	Orphan drug is considered ***registered*** at step 1	Orphan drug is considered ***available*** at step 2	Orphan drug is considered ***accessible*** at step 3
Indicators	**Direct indicators to explore access to orphan drugs**		
	Number of registered orphan drugs per country	Number of priced orphan drugs per country	Number of reimbursed orphan drugs per country
	Indirect indicators to explore access to orphan drugs		
	–	Delay in days for registered but non-priced drugs	Inter-country agreement rate, Inter-country Cohen's kappa agreement coefficient
Factors	EU integration status, Total health expenditure per capita, Population size		

innovative therapies a serious obstacle. Nevertheless, ongoing EU integration in this region and improved opportunities for cross-border healthcare require in-depth analysis of access to orphan drugs in these countries and reassessment of national health policies in the field of rare diseases and orphan drugs.

This study aims to compare orphan drugs access among a selected sample of Balkan countries: five EU Member States (Bulgaria, Croatia, Greece, Romania, Slovenia) and two EU Candidates (Serbia, Montenegro). We critically analyse variations in terms of registered, priced and reimbursed orphan medicinal products in these countries.

2. Material and methods

2.1. Scope of study

The comparative analysis was based on a cross-sectional study. It included medicinal products which had an active orphan designation under the Regulation (EC) 141/2000 [1] and were market authorised on January 1, 2017. The list of orphan drugs available on EU level was extracted from EMA's Register of orphan designations and Register of medicinal products [11,12]. Market authorised orphan medicinal products without prior orphan designation in the EU and medicinal products for which orphan designation had been withdrawn or expired, were excluded from the scope of the study.

2.2. Data collection and analysis

Access to orphan drugs was defined as an opportunity of timely and reimbursed medicinal treatment. In this context, access was considered as a 3-step process, combining market authorisation (centralised for EU Member States and national for non-EU Member States), availability (pricing according to national legislation), and reimbursement by public funds [29,30]. Under this definition, orphan medicinal products were classified into three categories: registered, available, and accessible (Table 1). A list of competent authorities per country was prepared. Official websites and publicly available documents were checked for relevant information on market authorisation, pricing, and reimbursement status of the orphan drugs studied (Table 2).

Following this 3-step process, a set of direct and indirect indicators was applied to explore access to orphan drugs at each stage (Table 1). Numbers of registered, priced, and reimbursed orphan drugs per country were produced by consecutive filtering at the phases of market authorisation, availability, and reimbursement (yes or no). The final outcome contained orphan medicinal products that are considered accessible to rare disease patients at national level. This last indicator was outlined with regard to three factors that previous studies confirmed to impact access to orphan drugs: EU integration status, total health expenditure per capita, and population size [4,7,8,30–32]. Data regarding total health expenditure per capita were extracted from the WHO Global Health Expenditure database [33], whereas data regarding population size were extracted from the World Bank database [34].

Three indirect indicators were additionally used to assess orphan drug access. Analysed orphan medicinal products were split into two subgroups. Access delay was calculated for the orphan drugs that were market approved by EMA, but were not priced in any of the countries studied. Delay in days was quantified as the time period from the date of market authorisation recommendation by EMA to February 1, 2017. Delays in diagnosis and treatment are found to be indicators of substantial importance in

Table 2
Data sources per country.

Country	3-step process of access to orphan drugs		
	(1) Market authorisation	(2) Pricing	(3) Reimbursement
Bulgaria	EMA [12]	National Council on Prices and Reimbursement of Medicinal Products [13]	National council on prices and reimbursement of medicinal products [13] National Health Insurance Fund [14]
Croatia	EMA [12]	Croatian Health Insurance Fund [15,16]	Croatian Health Insurance Fund [16]
Greece	EMA [12]	Ministry of Health of Greece [17]	National Organisation for Medicines of Greece [18]
Montenegro	Agency for Medicines and Medical Devices of Montenegro [19]	Agency for Medicines and Medical Devices of Montenegro [20]	National Health Insurance Fund of Montenegro [21]
Romania	EMA [12]	Ministry of Health of Romania [22]	National Health Insurance House of Romania [23]
Serbia	Medicines and Medical Devices Agency of Serbia [24]	Government of the Republic of Serbia [25]	National Health Insurance Fund of Serbia [26]
Slovenia	EMA [12]	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia [27]	Health Insurance Institute of Slovenia [28]

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