The Challenges of Patient Access for Rare Disease Therapies in Hungary and Europe

Doctoral thesis

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1. Introduction

Funding of high-cost orphan medicinal products (OMPs), indicated for rare diseases (RDs), is an increasing challenge for the public health care system of the developed countries such as Hungary and the other member states (MSs) of the European Union (EU). Approximately, 8.000 rare ailments have been identified so far. However one disease is characterized by extremely low prevalence or incidence rates - the total number of RDs might exceed 6-8% of the population – that involves more than 300 million patients worldwide, 27-36 million in the EU, 600.000 cases in Hungary.

95% of the RDs fail to hold any authorized medical treatments. More than 80% is due to rare genetic etiology, 60-70% of the cases to count with neurological symptoms.

The extremely low patient number, the lack of hard clinical endpoints and appropriate evidence baseline, or the special ethical issues are significant limiting factors regarding both the medicine and the health-economical aspects.

The OMP is a complex notion – based on the entity of science, authorization, pricing, financing and access. Usually, the prices of OMPs are significantly higher than pharmaceutical prices at

common diseases. It is difficult to measure the efficacy and cost-effectiveness of OMPs, therefore the implementation of transparent criteria for pricing and reimbursement is a great challenge. Ultimately, the patient access for the indicated therapy is compromised.

The unaffordable prices and the increasing expenditure on OMPs challenge the sustainability of public health care funding in several member states of the EU.

Particularly, in case of these medicines the real world data hold high priority, which provide relevant information on the individual patients derived from real institutional/ hospital/ domestic circumstances by differing from the clinical research and studies.

The clinician intends to give the ”appropriate therapy” for the rare patients, however in the 21st century medicine, the interpretation of this phrase is complex, assuming the factors of the person (the patient) and of its narrow and wider social area (family, society). Regarding a certain therapy, the emphasis is not only on the availability or the opportunity, but also we must emphasize the indication based on rationality.

2. Objectives

The aim of our research is to analyse the availability, patient access and the burden of public funding in Hungary and in the MSs characterized by different attributes in the EU.

2.1. The patient access and the public funding of OMPs in Hungary

2.1.a) In 2012, how many OMPs are available in the frame of social insurance in Hungary?

2.1.b) What kind of domestic financial methods exist? Do the patient access and the ”real-world data” collection depend on the varied financial methods?

2.1.c) What is the extent of the cost commitment of the public financed OMPs? For how many RD patients annually?

2.1.d) What part of the Hungarian OMPs with social insurance is indicted for the treatment of neurological ailments? What is the patient number? What is the extent of the cost commitment of these orphan products?

2.2. The availability of OMPs and the national public expenditures within the EU.

The main aspects of our study were to map the availability and to analyse the public financial methods, as well as the burdens of cost commitments focusing on 83 OMPs authorized by the European Medicines Agency (EMA) in 8 MSs characterized by different economical and demographic status and to position our country. The analysed countries were as follow: Austria, Belgium, Bulgaria, Czech Republic, France, Poland, Hungary and Slovenia.

2.2.a) Does the number of the accessible OMPs clearly depend on the economic status of the MSs? (Do fewer OMPs are available in the lower-income countries?)

2.2.b) Are the OMPs covered by standard or unique reimbursement methods, in- or out-patient care divisions in the various countries?

2.2.c) Regarding the EU analysis of budget impacts, do any correlations exist between the national economic status and the range of the national public expenditures?

2.2.d) In connection with the patient access of determined OMPs, does inequity appear at national level?

3. Methods

Data collection of our ”orphan work team” derived from the following sources: academic sectors, research institutes, competent and relevant marketing/financial authorities, governmental bodies, other background institutions of 8 MSs of the EU.

Qualitative data were provided by 8 MSs: Austria, Belgium, Bulgaria, Czech Republic, France, Hungary, Poland and Slovenia. Qualitative and quantitative data were provided by 7 MSs: Austria, Belgium, Bulgaria, Czech Republic, Hungary, Poland and Slovenia.

The demographic and economic data (population size, current exchange rates, GDPs) were taken from Eurostat website. Austrian demographic data were not available on the Eurostat website; therefore we gained them from the OECD database.

The methods are detailed in accordance with the objectives.

3.1. The analysis of the availability and the public financing of OMPs in Hungary.

3.1.a) Based on the Orphanet website, we selected the authorized OMPs from the Hungarian public drug list of the National Health Insurance Fund (NHIF) and financed by the public health care system in 2012. We requested the official data (patient number, financial details) from the subgroup of this kind of OMPs that are not subsidized by the standard reimbursement system, but have been allowed to cover by special financial techniques on individual basis.

3.1.b) The medicines were listed according to financial methods and categories: **standard** (subsidized by hospital and/ or pharmaceutical budget) and other **special** reimbursement techniques (e.g.: on individual basis

3.1.c) Patient numbers and cost commitments per product were gained and calculated from the NHIF database. Furthermore, the summarized patient numbers and financial costs were taken cumulatively within each financial technique.

3.1.d) We detected what percentage of the total pharmaceutical expenditures were subsidized for the OMPs indicated for neurological ailments in 2012.

3.2. The availability and the national public expenditures of the OMPs in the EU

3.2.a) We found 83 medicines based on the list OMPs published at the Orphanet website and validated the list based on the pharmaceutical database of EMA.

3.2.b) The following specific information related to the 83 OMPs were requested in 8 MSs:

- Which orphans are available by standard (within hospital and/ or pharmaceutical budget) or by other special reimbursement techniques (e.g.: on individual basis) in some MSs?
- The public reimbursement methods were classified in 4 categories:

  (1) ***Standard reimbursement in the frame of in-, and out-patient care*** (Medical prescription basis, related to retail pharmacies or institutional use)

  (2) ***Standard reimbursement in the frame of out-patient care*** (Medical prescription basis, related to retail pharmacies)

  (3) ***Standard reimbursement in the frame of in-patient care*** (Institutional use)

(4) ***Special financial methods*** –based not on the standard reimbursement system, but depend on the individual requests.

3.2.c) From the national databases of 2013 and 2014, the patient numbers and the cost commitments per orphan products were obtained, furthermore the summarized patient numbers and public costs were cumulated within the financial methods. The national annual public expenditures for 2013 and 2014 were calculated per capita and were quantified as the proportion of *national GDP, total pharmaceutical and health care budget*. We converted the spendings into EUR by applying the annual currency exchange rates based on Eurostat data.

3.2.d) We compared public expenditure on ten specific indicator OMPs per 100.000 inhabitants in 2013 and 2014. We intended to select a representative sample of OMPs based on different attributes as field of the indication, existing therapeutic alternative, relative effectiveness (potentially curative/non-curative treatment), rarity (orphan/ultra-orphan status) and cost commitment. A heterogeneous group of OMPs was collected, including idursulfase for mucopolysaccharidosis type II., rifunamide for Lennox–Gastaut syndrome,

romiplostim for idiopathic thrombocytopenic purpura, trabectedin for sarcomas and ovarian neoplasms, nelarabine for special types of leukaemia or lymphoma, sildenafil for pulmonary hypertension, alglucosidase alfa for glycogen storage disease type II, icatibant for inadequate or non-functioning C1-Inhibitor protein and sapropterin for phenylketonurias, and eculizumab for paroxysmal nocturnal haemoglobinuria or for atypical haemolytic uremic syndrome.

4. Results

The results are detailed according to the objectives.

4.1.a) In 2012, **36 products** were available in the frame of the social insurance system – 33 products were characterized as orphan drugs.

4.1.b)

I. OMPs subsidized on reimbursement basis: in the frame of out-patient care, related to medical prescription and retail pharmacies:

- *Only in the classical reimbursement category:* **5 products** with the subsidy rate of 100% , **1 product** with 90%
- Most of the medicines, namely **19 products** were allowed to be financed by *special reimbursement technique based on individual request.* We must emphasize that this method is a unique opportunity, not an automatism of the social reimbursement system.
- **8 products** were allowed to be subsidy by both - standard and special - reimbursement methods depending on the indication.

II. OMPs subsidized by itemized financing: in the division of in-patient care, related to hospital use: 3 products.

4.1.c)

I. OMPs subsidized on reimbursement basis: within out-patient care, related to medical prescription and retail pharmacies: In 2012 the Hungarian NHIF subsidized **11,8 billion HUF** for 14 products, for **2337 patients** in the frame of standard reimbursement. 27 db OMPs with **4,1 billion HUF** were financed for **294 patients** by special financial method.

II. OMPs subsidized by itemized financing: in the division of in-patient care in relation to hospital use: the total annual cost for **29 patients was 387 million HUF.**

In Hungary, the OMPs' total expenditure range was **530 000 – 165 million/capita** in 2012.

The analysis of the data of OMPs financed by special reimbursement

According to the Budget Law in 2012, the target amount of the special reimbursement budget was 3 billion HUF, which had to be revised up to **6.3 billion HUF**. Only the public expenditures of the 5 enzyme replacement therapies exceeded the **3 billion HUF.**

4.1.d) Among the 33 reimbursed OMPs, **14 products** were indicated for rare neurological diseases in Hungary. In total, **17 authorized medicines** were authorized for rare neurological ailments in 2012.

I. OMPs subsidized on reimbursement basis: in out-patient division, related to medical prescription and retail pharmacies:

Only in the classical reimbursement category: **1-1 product** with the subsidy rate of 100% and 90%

- By *special reimbursement technique based on individual request:* ***13 products +1 product*** in off-label use. Among these top 10 highest cost therapies, 9 were authorized for rare neurological diseases.

II. OMPs subsidized by itemized financing: in the division of in-patient care, related to hospital use: ***2 products.***

The 30% of the RD reimbursement were paid for rare neurological ailments. Except one product, the subsidy rates were 90%, these medicines were reimbursed to 100%. The total expenditures of the highest cost medicines authorized for rare

neurological diseases exceeded 4.5 billion HUF, this amount made 1.4% of the total pharmaceutical budget in 2012. The average therapeutic cost range dispersed 280 000 – 74 million HUF / per capita in 2012.

4.2. The availability and the national public expenditures in the European Union

4.2.a) In 2015 29.4–92.8% of the 83 OMPs were available with any kind of public reimbursement in participant countries including special reimbursement on an individual basis.

4.2.b) **Standard reimbursement** through retail pharmacies and/or hospitals was applied from **0 to 41%** of OMPs.

4.2.c) In the 7 participant countries total public expenditures on OMPs were increased from **1.13–21.95 €/capita** (mean: 7.36 €/capita) in 2013 to **1.69–25.04 €/capita** (mean: 8.66 €/capita) in 2014. The average spending per capita in 2013–14 was ranged between1.41–23.50 € (mean: 8.63 €/capita). The absolute spending per capita showed **16.7 fold** differences between countries with the highest and lowest spending. Average expenditures on OMPs ranged between **2.25–6.51%** of

the public pharmaceutical budget and **0.44–0.96%** of public health care expenditures in 2013–14.

4.2.d) Compared to the average spending of the participating countries, the Western-European countries and Slovenia showed significantly higher spending than the CEE countries. Wealthier countries spend more per capita on ODs than lower-income countries.

5. Conclusions

Hungarian findings

5.1.a) Regarding the availability of the OMPs, the median percentage of 3 consecutive years (2010: 67%, 2012: 52%, 2015: 45%) is 55%. Consequently, the **55%** of the current authorized OMPs are available in Hungary.

5.1.b) In 2012, the reimbursed OMPs were reimbursed by 3 types of public financial methods (classical reimbursement, special reimbursement in out-patient division, itemized financing). A dominant technique was the special reimbursement, which was not considered as a standard method, but a unique opportunity based on individual request for subsidy. Notably, this financial technique proved to be the optimal way to collect ”real-world” data.

5.1.c) Numerous discrepancies were stated during the analysis of the orphans’ cost commitment:

• 50% of the annual budget of special reimbursement was covered for 5 high-cost enzyme replacement therapies (those were only 2% of the whole special reimbursed product group).

• 70% of the annual budget was subsidized for 27 OMPs (11%

of the whole special reimbursed product group).

• 30% of this special budget was provided for the 223 other medicinal products (87% of the special reimbursed medicinal group).

5.1.d) In Hungary, 50% of the public financed OMPs was indicated for rare neurological diseases. 30% of the RD reimbursement was spent for the treatments of rare neurological ailments. Consequently, the health-economic importance of the medicines authorized for rare neurological diseases is unquestionable.

5.2. Analyzing the MSs of the EU, we came to the following conclusions:

5.2.a) The availability of OMPs is not to clearly associate with the economic status, however the number of orphans financed by public health care budget decreases regarding the East-West axis.

5.2.b) Standard and special reimbursement techniques in out-, or out-patient care play different roles in participant MSs. In

many countries the reimbursement is linked to institutional funding – contrary to Hungary.

5.2.c) The absolute spending on OMPs is clearly associated with the economic status of countries. According to our findings, the spending on OMPs as a proportion of GDP, public pharmaceutical and health care expenditure was not higher in lower-income countries compared to those with higher-income, which also indicates substantial differences in patient access to OMPs in favour of higher income countries. However, the relatively small markets (e.g.: Slovenia) are not characterized with the lowest prices. The limited advocacy of the lower population countries might be the reason of this finding.

5.2.d) Having regard to the analysis of the inequity of patient access, we shall draw the following conclusion: the patient access reveals the Western-Eastern degressive axis.

6. List of own publications

Publications – serving as the basis for the thesis:

- Szegedi M, Zelei T, Arickx F, Bucsics A, Cohn-Zanchetta E, Fürst J, Kamusheva M, Kawalec P, Petrova G, Slaby J, Stawowczyk E, Vocelka M, Zechmeister-Koss I, Kaló Z, Molnár MJ. (2018) The European challenges of funding orphan medicinal products. Orphanet J Rare Dis, 13:184. **IF: 3,687**
- Zelei T, Molnar MJ, Szegedi M, Kaló Z. (2016) Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. Orphanet J Rare Dis, 11(1): 72. [1]Due to the type of bulletin, it will not be listed (IF: 3,478)[1]
- Szegedi M, Kosztolányi Gy, Boncz I, Molnár MJ. (2016) The financing of medicines for rare neurological diseases. Ideggyogy Sz, 69(1-2):37-45. **IF: 0,322**
- Szegedi M, Molnár MJ. (2015) The rare diseases and the indicated orphan drugs. Pediatrics Review, 1-4. IF: 0,0
- Szegedi M, Molnár MJ, Boncz I, Kosztolányi G. (2014) Shift of focus in the financing of Hungarian drugs. Reimbursement for orphan drugs for treating rare diseases: financing of enzyme replacement therapy in Hungary. Orv Hetil, 155(44):1735-41. IF: 0,0

Summarized impact factors related to publications for the thesis: **4,009**

Further publications:

Péntek M, Herczegfalvi Á, Molnár MJ, Szőnyi LP, Kosztolányi G, Pfliegler G, Melegh B, Boncz I, Brodszky V, Baji P, Szegedi M, Pogány G, Gulácsi L. (2016) Disease burden of Duchenne muscular dystrophy patients and their caregivers. Ideggyogy Sz, 69(5-6):183-93. **IF: 0,322**

Summarized impact factors: **4,331**

Book chapter:

Molnár MJ, Szegedi M. A ritka kórképekben szenvedő betegek biztonsága. In: Baranyai Zs - Harsányi L (szerk.), Betegbiztonság. Medicina, Budapest, 2016: 239-252 Hungarian