Evaluation of health technologies used in the treatment of rare diseases

Theses

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1 Background and problem statement

The valuation and pricing of health technologies differs from the traditional goods and services which are defined within an environment of classic market mechanisms. From the economical perspective, goods and services are valued at a price that is considered to be acceptable for the consumers. Therefore, the price of these goods and services is defined by the supply and the demand on the market. Due to market failures the valuation of innovative pharmaceuticals is a more complex issue. The process of defining the value and the price of innovative pharmaceuticals differs mainly due to the patent protection that creates a monopoly status, the high cost of innovation and the third party payer (e.g. national insurance fund) that has a prominent role in the market transactions. The actual price of these products is defined through a negotiation between the pharmaceutical manufacturer (the seller) and a third party payer (the buyer). This process is supported by the different tools of health economics. Despite the fact that this field of science is relatively new, several methods had been developed with the aim of setting the prices of health technologies (Neumann et al., 2018).

A frequently followed concept of health economics in case of innovative technologies is the value based pricing approach (Drummond et al., 2015). The following question is raised: What is the value of a new pharmaceutical product or other health technology? According to the principles of health economics the value is defined based on the incremental health gain associated with the new health technology compared to the current standard of care. The health gain is defined by the combination of improved quality of life and/or the life years gained and by the cost of the medical incidents avoided during the application (Drummond et al., 2015). This concept has become widely used in developed countries mainly because the data and information required for such evaluation are available in many cases.

Lately, the focus of pharmaceutical innovation has changed, which also created new challenges in the assessment of the value as well. Several pharmaceutical manufacturers started to focus on those niche markets where the unmet medical need is higher. One prominent example for this is the field of rare diseases.

The rare diseases relate to a highly heterogenic patient population. These diseases are classified only by their prevalence in the population and by their severity. There is no universally accepted definition. Different regions, countries and organizations have different cut-off points for the rarity to include a disease to the group of rare diseases (Richter et al., 2015).

As a result of the low number of patients the research and development, the authorization of the procedures for diagnosing rare diseases and the pharmaceuticals to treat diagnosed patients have relatively higher costs. Therefore, in a traditional regulatory environment there was a high risk of poor return on investment for such goods and services. For these reasons the pharmaceutical industry was not focusing on the market of rare diseases in the past. The term "orphan medicinal products" is generally used for the technologies applied for the diagnosis, prevention and treatment of rare diseases. The pharmaceuticals used for the treatment of rare diseases are called "orphan drugs" (European Commission, 2018). The term „orphan" refers to this neglected and abandoned status of patients on this field. The traditional market authorization and pricing and reimbursement procedures did not foster the pharmaceutical innovation in this field. The three underlying reasons were: 1) it is not realistic to conduct a randomized clinical trial with the traditionally required large number of patients, 2) the low number of patients leads to a high risk of poor return on investment and 3) if the prices set higher to decrease the risk of poor return on investment, the third party payer might cannot afford to reimburse the pharmaceuticals.

Due to the highlighted reasons incentives were introduced for the research and development of orphan drugs, mainly in the developed countries. These incentives were first provided in the United States in 1983

and then in 1991 in Singapore, in 1993 in Japan, in 1997 in Australia and in 2000 in the European Union (Orphanet, 2018a).

According to the European Union, those products can be labelled as orphan drugs, which meet a number of criteria: 1) it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; 2) the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; 3) there is no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

There are a number of reasons why there are more and more treatment options for rare diseases such as the changing regulatory environment, incentives for the industry, easier authorization process, changing industrial strategies and scientific development. Still the process of defining the value and the price of these products is very challenging. Currently those health technology assessment frameworks which are traditionally used for pricing and reimbursement decisions might not be able to appropriately define the value of an orphan drug. Several times positive reimbursement decisions are being made also in case of those drugs where only limited evidence is available on efficacy, safety or cost-effectiveness. In terms of budget impact, the financial burden on the payer might be acceptable due to the low number of patients, but the treatment costs per patient could be extremely high. Nowadays the budget impact for all orphan drugs is becoming higher, however, the actual impact on the health system is less known due to the different financing mechanisms. The concept of equity appears to be an important criterion in theory, but the explicit definition of how to consider equity in decision is not defined appropriately.

Due to these reasons, the health technology assessment of orphan drugs needs further and more in-depth investigation. When the evaluation of

these technologies is not possible with the traditional framework, then the applied criteria and tools should be re-structured and re-defined and if necessary, new aspects should be defined for the evaluation.

The objective of this research is to explore the applicability of the current health technology assessment frameworks in case of orphan drugs and to reveal the potential constrains of their application. This research attempts to provide recommendations to re-structure or re-consider existing criteria that may lead to improve the transparency and the consistency of decision making. Furthermore, the research attempts to introduce new criteria, which could be used in the current framework for the assessment of the health technologies. Ultimately the objective of this research is to improve the assessment of orphan drugs with a special attention to the Hungarian context in order to strengthen the evidence base of decisions on the public resources.

2 Applied methodology

The dissertation was based on four independent researches carried out during the doctoral program.

2.1 Systematic literature review to investigate the disease prevalence of Sanfilippo syndrome

To investigate the methodology of studies relevant to the clinical burden of rare diseases a systematic literature review was conducted on a selected rare disease. The study focused on epidemiological studies. The selected disease was the Sanfilippo syndrome. The primary objective of the study was to review the applied methodologies of the epidemiological studies in a disease where national registries are not available and where neonatal screening tests are not widely applied. Based on the identified studies we also defined the prevalence of the disease in different regions of the world (Zelei et al., 2018).

The systematic literature review was conducted and reported in compliance with the internationally accepted PRISMA guideline (Liberati et al., 2009, Moher et al., 2009). In the first step, structured searches were conducted in the following databases: Medline, Embase, Cochrane Database of Systematic Reviews, Academic Search Complete, CINAHL, CRD Database. In addition, the databases and websites of relevant rare disease organizations were reviewed to identify additional studies. The title and abstract screening of the hits was conducted by two independent researchers. The full text version of the potentially relevant papers was reviewed by one researcher. Based on the full text review the final pool of relevant articles was defined. Articles without relevant data were excluded. From the included studies the relevant data was extracted to a pre-defined structured Microsoft Excel spreadsheet. Qualitative synthesis of the research findings was performed, as quantitative synthesis (meta-analysis) of the collected disease prevalence data did not promise substantial added value.

2.2 Systematic literature review on the evaluation criteria of orphan medicines

This study attempted to systematically collect those evaluation criteria which are relevant for the treatments of rare diseases in case of a health technology assessment process. In the past, no comprehensive study was conducted in Central and Eastern Europe that investigated the standard HTA framework and considered additional criteria for the assessment of orphan drugs. The primary objective of the study was to provide a well-established guidance for the fine-tuning and re-considering the traditional framework of the health technology assessment, according to the specific characteristics of the rare diseases. The search was conducted globally, but special attention was given to the Central and Eastern European region, to draw conclusions that are more relevant to the Hungarian context. Formerly, such focus on this region was a gap in the literature.

The systematic literature review was conducted and reported in compliance with the internationally accepted PRIMA guideline (Liberati et

al., 2009, Moher et al., 2009). In the first step, structured searches were conducted with PubMed and Scopus search engines. The title and abstract screening of the hits from different databases was conducted by two independent researchers. The full text version of the potentially relevant papers was reviewed in the next steps. Based on the full text review, the final pool of relevant articles was defined. Articles without relevant data were excluded. From the included studies the relevant data were extracted to a pre-defined structured Microsoft Excel spreadsheet. The relevant information were collected according to the different major categories of the traditional health technology assessment: efficacy, effectiveness, cost-effectiveness, budget impact and equity. Every potential information for each criterion was collected including the usefulness of the criteria, its limitation and its potential further improvement. Furthermore, any additional criteria that could not be categorized to the abovementioned criteria were collected separately. The study eventually collected and comprehensively described all potential value drives that could be used in case of rare diseases. Qualitative synthesis of the findings was performed as the nature of the information collected did not allow for quantitative synthesis or further meta-analysis.

2.3 Data request from the National Health Insurance Fund of Hungary to estimate the budget impact of orphan drugs

Since there is a limited evidence on the budget impact of orphan drugs a data request was submitted to the National Health Insurance Fund of Hungary that is responsible for allocating the public resources for the pharmaceutical products.

In the first step, the list of orphan drugs was defined which had marketing authorization in the European Union. The Orphanet website was used for this purpose, and 83 orphan drugs were identified. This list was double-checked on the website of the European Medicines Agency.

One objective of the data request was to define how many of the 83 orphan drugs are available in Hungary. We considered those drugs available

which were reimbursed from public resources to the patients. The second objective was to define the cumulative budget impact of those orphan drugs that are publicly reimbursed. The budget impact was defined in accordance with the expenditure of the National Health Insurance Fund in 2013 and 2014. We considered all form of reimbursements such as standard reimbursement through retail pharmacies or hospitals and special patient level reimbursement based on individual requests.

The number of available drugs were compared to data available from other countries published in the literature. The cumulative budget impact of orphan drugs was compared to the total expenditure on pharmaceuticals and to the total healthcare expenditure in Hungary. The expenditure on pharmaceuticals and the total healthcare expenditure was defined from the data published by the Hungarian Central Statistical Office. The percentage of orphan drugs available was compared to data available from other countries. Eventually, the study defined the financial burden of orphan drugs from the perspective of the public payer.

2.4 The methodology of investigating the association between the incremental cost-effectiveness ratio, the disease prevalence and the incremental health gain of orphan drugs

To assess the cost-effectiveness of orphan drugs, we selected the United Kingdom as a benchmark, since they have been using explicit cost-effectiveness thresholds for a long time and have made the analyses public. Therefore, these are freely available, researchable, and easy to be analysed. In our study, we investigated that how many orphan drugs are cost-effective at the standard threshold, and whether there is a correlation between the prevalence of the disease being treated and the incremental cost-effectiveness ratio (ICER).

In the database of Orphanet we identified 84 orphan drugs with marketing authorization rights in 2015 December. Publicly available cost-

utility analyses from the United Kingdom were searched. The sources included the reports of relevant public institutes: National Health Service, National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), CRD/CHE Technology Assessment Group of University of York and scientific publications. In addition, we performed Google searches to identify further relevant analyses.

The identified reports were downloaded in full text. Data was extracted to a structured Microsoft Excel spreadsheet. ICER values and incremental QALY gains were systematically collected for all orphan drugs from the identified assessment reports. Additionally, the collected data included the source of data, year of publication, indication, applied comparator therapy, timeline of the analysis and applied sensitivity analysis. In every analysis we considered the base case as the relevant scenario.

Point prevalence estimations of the target diseases were obtained from Orphanet prevalence report (Orphanet, 2018b).

In the first step, ICER values were plotted against the disease prevalence. The association of the two variables were tested. We applied the least squares method to fit a curve and we investigated the coefficient of determination (R^2). In the second step, ICER values were plotted against the incremental health gains and the disease prevalences were symbolized by the size of the data points. The hypothesis was that higher incremental QALY gains and/or lower disease prevalence is associated with higher ICERs. This hypothesis was tested with an index calculated according to the following equation:

$$\text{Pricing index} = \frac{\text{"incremental QALY gain per patient"}}{\text{"disease prevalence" x "ICER"}}$$

The selected orphan drugs were compared according to this index. Based on the relative values the following categories were defined: 1) Overpriced, 2) Fair priced, 3) Under priced. In scenario analysis the large

scale difference in disease prevalence values was attenuated by logarithmic transformation and its influence on the results was investigated. Since this method is not generally applied, the limitation of the method is that only the included drugs can be compared to each other, the price is judged relatively for the current sample.

3 Results

3.1 Measuring disease prevalence

- The prevalence of Sanfilippo syndrome was measured with different methods. These methods were different in terms of the terminology but also in terms of the calculation method, therefore the interpretation and the comparability of the results is limited. The major conclusion of the research is that in case of rare diseases the methodology of the relevant studies should undergo a critical review.
- From the study designs and related calculation methods of the epidemiological measures identified during the systematic literature review on the epidemiology of Sanfilippo syndrome, the Dx method used to estimate lifetime risk at birth can be proposed,
- furthermore, if we can apply sufficiently long follow-up period to make sure that the disease can appear in all individuals included in the study, then the cumulative incidence measured in the birth cohort also provides reliable result. This is especially true in those cases where the disease manifests right after birth.
- According to the results of studies identified by the systematic literature review, in each birth cohort from 100 000 people only a few will be diagnosed with the Sanfilippo syndrome during their life. If the life expectancy of patients is below the life expectancy of the general population (which has also been proven), the point prevalence of the disease at any given point in time cannot exceed the reported values. Therefore, the results undoubtedly prove that Sanfilippo syndrome is a rare disease, i.e. in Europe it affects less

than five people out of 10,000 people. In addition, the analysis provided information on the frequency and distribution of the four subtypes (A-D), A and B were more prevalent depending on the area, while subtype C and D are extremely rare in all studied regions.

- In the absence of reliable statistics such as national or international patient registries or screening databases, the systematic literature review is an appropriate tool for estimating the prevalence of a rare disease. Systematic collection and evaluation of information accumulated in scientific literature can provide evidence both in national and international comparison.

3.2 Measuring disease progression

- There was very little data available in the literature regarding the progression of Sanfilippo syndrome.
- The identified clinical parameters are difficult to use as surrogate endpoints, and their relationship with hard endpoints (e.g. survival) can be inaccurately estimated.
- Information on the hard disease progression measures is incomplete, limited number of studies published relevant data. Subtypes A and B appear in early childhood (3-5 years of age) and patients have very poor life expectancy (~ 15 years). Subtypes C and D occur somewhat later (5-10 years of age) and patients' life expectancy is also slightly longer. On patient survival, as a hard endpoint, few good quality data was available, furthermore we should apply too long follow up period to make it measurable, and so it cannot be used as a clinical trial endpoint.
- Based on these results, the primary role of hard endpoints in case of rare diseases can be rarely expected, instead, a composite endpoint including most severe symptoms that describes well the progression of the disease may be suggested as a clinical trial endpoint.

3.3 Budget impact of orphan drugs

- Based on the international literature and the results of data request in Hungary, it can be concluded that countries spend a significant proportion of their pharmaceutical budget on orphan drugs, especially since this spending refers to a very small number of patients.
- According to the literature data, the drug group places an increasing burden on public payers. Central and Eastern European countries reported access barriers.
- A few drugs produce a large part of the cumulative budget impact, for which budget impact analysis should receive a special attention.
- Sophisticated budget impact analysis is required for all orphan drugs, but especially for those with multiple indications or potential for off-label use. When new indications are introduced, new budget impact analysis is required.
- The Hungarian data are like the literature data, they are comparable both in their extent and in their increasing tendency. In Hungary, the share of orphan drugs in the public pharmaceutical budget was 3.15% in 2013 and 3.94% in 2014. There was some lagging behind the western countries in the number and proportion of medicines being reimbursed.
- Overall, it can be concluded that the reimbursement of orphan drugs is now a major burden on public payers, consequently, the reimbursement of certain drugs because of limited budget impact can no longer be maintained.

3.4 Cost-effectiveness of orphan drugs

- The results of the systematic literature review and the data collection in the United Kingdom have shown that certain orphan drugs can meet the standard cost-effectiveness criteria, as out of 31 drugs, 9 had

ICER below the threshold. Therefore, the uniform elevation of the cost-effectiveness threshold does not seem to be justified.

- Consideration may be given to establish an increasing threshold with decreasing disease prevalence, as drugs with exceptionally high ICERs typically belonged to ultra rare diseases.
- Social preference (i.e. willingness to pay) must be priced for rare diseases, because in many cases the reimbursement occurs along ICERs that are significantly higher than traditionally accepted thresholds. It should be emphasized that assessing willingness to pay is important, on the one hand, because of this we can make fair reimbursement decisions, and on the other hand it encourages manufacturers to develop more effective orphan drugs, furthermore, it creates a transparent and predictable regulatory environment.

3.5 The relationship of disease prevalence and incremental health gains with the cost-effectiveness ratio

- The role of target disease prevalence and the role of incremental health gains provided by the new drug in pricing of orphan drugs cannot be justified. In the investigated drug group, ICER values (past pricing decisions) were basically influenced by other factors.
- The results of our research have shown that the ICER values of orphan drugs can be compared and evaluated with a simple index calculation methodology in respect of the two studied parameters. Since previous studies did not investigate the relationship between these parameters, there is no reference point available, and the comparisons could only be made relative to each other. Although the relationship could not be established, these two parameters may play a role in the evaluation of orphan drugs in the future.

3.6 Equity aspects

- Our research confirmed that equity arguments play an extremely important role in determining the value of orphan drugs.
- Based on the systematic literature review it can be stated that there is no uniform equity concept, several theories play role in supporting the equity arguments. The analysis provided an opportunity to organize and interpret the equity theories, but deeper analysis of these and presentation of empirical evidence has not been occurred so far.
- There is no detailed recommendation in the literature to establish the measurability of the equity aspect and its practical application in the framework of health technology assessment.
- On a theoretical basis, the prevalence of the disease is related to equity arguments, so this variable can be considered when the equity aspect is evaluated.
- On the basis of equity, the severity/life-threatening nature of the disease or the availability of treatment alternatives can also be assessed.

3.7 Additional evaluation criteria

- The results of the research have highlighted the need to integrate several criteria in the evaluation process that have been examined so far inadequately or with inappropriate weight.
- In connection with the disease, consideration should be given to its severity / life-threatening nature and the existence of other treatments in the disease area. In connection with the new therapy, consideration should be given to the nature of the therapeutic effect (reversing or only slowing the progression), the degree of scientific research and development, innovation and production complexity associated with the new product.
- However, in most cases, there are no arguments based on strong evidence to support the additional aspects. As a result, the practical

application of these criteria during health technology assessment is also limited.

- In addition, the relationship of additional aspects with existing technology assessment criteria has not been investigated adequately, i.e. whether a value-bearing factor is considered multiple times or not (e.g. quality of life that is taken into account in cost-effectiveness calculations and severity of disease as an additional aspect).

3.8 Recommendations for developing technology assessment framework

The standard framework of health technology assessment has limitations in the case of therapies for rare diseases, so the revision of previously established frameworks has become necessary. With my results, I have sought a deeper understanding and analysis of the classical aspects and I tried to recommend the inclusion of additional criteria in the evaluation process.

The prevalence of the target disease is not investigated by the standard technology assessment criteria, because in the case of traditional diseases this aspect is not considered as a value bearing factor. Currently, in the field of rare diseases, the investigation of the disease prevalence is primarily necessary to obtain the orphan designation. At the same time, it can be assumed that the prevalence of the disease is also related to the equity aspects in addition to the burden of disease and the budget impact. Therefore, I recommend taking into account the prevalence of the target disease when evaluating the drugs for rare diseases, i.e. the rarer the disease, the higher the premium for a particular treatment for the disease. If we accept this and the equity aspects continue to have significant weight during the evaluation of orphan drugs, then the reliability of the potentially related disease prevalence data will come to the fore, and the methodological recommendations for their estimation methods will be more appreciated.

Using the logic applied by Paulden et al. (2015) as a starting point, based on my results the factors listed in Table 1 can be considered during the health technology assessment of treatments of rare diseases.

Table 1. Factors to consider in the health technology assessment of treatments of rare diseases

Disease-related factors	• Prevalence of the disease • severity/life-threatening nature of the disease • availability of treatment alternatives • identifiability of responders to treatment / heterogeneity of disease (existence of potential subgroups)
Treatment-related factors	• evidence of treatment efficacy or effectiveness • safety profile of treatment • nature of the therapeutic effect (reversing, stabilizing or only slowing the progression) / magnitude of treatment benefit • „bridge" therapy: the procedure allows patients to reach definitive treatment (e.g. transplantation) • innovative profile of treatment • manufacturing complexity
Economic factors	• cost-effectiveness of treatment (without mandatory threshold) • budget impact • number of indications • potential for off-label use
Social factors	• societal impact of treatment (i.e., indirect costs on families and caregivers) • equity in access to treatment • opportunity cost of treatment/ effect on distribution of health within the society

There are two ways to apply the listed criteria. The first is to create a multi-criteria decision analysis (MCDA) tool, in which a therapy is evaluated based on several explicit criteria (i.e. scoring), and then the scores of each criterion are weighted according to a predefined algorithm. Based on the aggregate score it is possible to decide whether a therapy is preferable

compared to other therapies or it is acceptable based on a pre-defined threshold. (Friedmann et al., 2018, Kolasa et al., 2018, Schey et al., 2017). Another possible way is to determine the size of price premium we consider realistic for the increasing values of each criterion. (Hall and Sireau, 2013). For example, a "price premium" can be determined which increases by disease prevalence bands or continuously and raises the acceptable price of the drug compared to the price set at the standard threshold, namely in case of rarer diseases higher price premium can be applied. Such monetary value is currently used only for incremental health gains. With different logic, both methods are suitable for considering additional aspects. Experience with the MCDA is more widely available, so this framework using the criteria above can be proposed as an appropriate method in the evaluation of health technologies used in the treatment of rare diseases.

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5 Publications related to the topic

Almási, T; Guey, TL; Lukacs, C; Csetneki, K; Vokó, Z; **Zelei, T.** Systematic literature review and meta-analysis on the epidemiology of propionic acidemia. ORPHANET JOURNAL OF RARE DISEASES (2019) (Accepted for publication)

Almási, T; Guey, L; Lukacs, C; Csetneki, K; Vokó, Z; **Zelei, T**, Systematic literature review on the worldwide epidemiology of methylmalonic acidemia with a focus on methylmalonyl-coa mutase deficiency VALUE IN HEALTH 21: Supplement 3 p. S441 (2018) (Poster abstract, Conference: 2018, November, ISPOR 21th Annual European Congress, Barcelona, Spain)

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