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Marketing Authorization of Orphan drugs in Turkey

N Buket Aksu[1*] and Birsen Eren[2]

*[*1]Faculty of Pharmacy, Pharmaceutical Technology Department, Istanbul, Turkey.*

[2]Chiesi Pharmaceutical, Regulatory Affairs Specialist and QPPV, Istanbul, Turkey.

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ABSTRACT

Rare diseases and orphan drugs, which are brought to the agenda as a consequence of growing population and increasing number of consanguineous marriages is a life-threatening social problem in Turkey too. Yet, many orphan drugs used in the treatment of orphan diseases are not given enough priority during the marketing authorization and pricing processes and there are ongoing studies for the identification of needs and priorities in Turkey. The Health Authority continues to identify rare diseases, prepare lists, draw road maps. For the sake of establishing cooperations, multi-center clinical researches of orphan diseases including our country are encouraged.

Keywords: Marketing authorization, Orphan diseases, Heterogeneity of treatment impacts, Drug legislation, Genetic X-linked

INTRODUCTION

Orphan diseases

Orphan diseases are the diseases with high morbidity and mortality which are encountered at a rate of less than 1/200,000 in ABD, 1/2000 in Australia and 1/50,000 in Japan. There are about 5000-8000 identified orphan diseases and every year, new ones are added. Although the frequency of orphan diseases differs based on the epidemiological situation of countries, they generally influence 10% of societies. Most of the orphan diseases threaten life and 80% of them have genetic origins [1-3].

Although the diseases that affect less than 200,000 people are considered orphan disease, every country is likely to define an orphan disease based on the prevalence ratios. For example, the diseases affecting fewer than 5 people in 10,000 are defined as orphan in Europe. In Brazil, it's defined as the disease affecting fewer than 65 people in 100,000 whereas in Taiwan, it is the disease common for fewer than 1 person in 10,000 [4-8].

Orphan drugs

The term orphan drug is used for drugs intended for the treatment of rare diseases. These drugs are referred to as orphan drugs because the number of patients affected by rare diseases is too low and the research, development and marketing of these drugs are not profitable. Development of orphan diseases is challenging for pharmaceutical companies because their market is small and research and development costs much exceed the profit obtained. Accordingly, in many countries orphan drug legislation is adopted in order to encourage producers to develop orphan drugs. Most frequent difficulties in the development of orphan drugs are: They can be administered to small number of patients, changing pathophysiology of diseases, not having a good understanding of the natural progress of the disease, not being able to find more than a few patients for clinical trials, not knowing the appropriate duration of treatment, unpredictability of the result, heterogeneity of treatment impacts, being have to give difficult decisions due to insufficient information and their high prices [9,10].

Patient access to orphan drugs

Although many orphan drugs are approved by competent authorities, not all of them are introduced into market. The basic reason of this problem is the financial challenges faced by small and medium sized companies in developing new drugs. Once an orphan drug obtains marketing authorization, the pricing and reimbursement decisions go through national health reviews. For reimbursement, efficiency and cost

Corresponding authors: N. Buket Aksu, Istanbul Altınbaş University, Faculty of Pharmacy, Pharmaceutical Technology Dept, 34140, Bakırkoy, Istanbul, Turkey, Tel: +905322767403; E-mail: buket.aksu@altinbas.edu.tr

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effectiveness of the drug are focused on. Because the prices of orphan drugs tend to be high, the existing approach related to reimbursement and its budget effect are not economically sustainable [11-13].

In many countries, orphan drug legislation is used for encouraging the research, development and marketing of orphan drugs. With its Orphan Drug Act of 1983, USA is the first in establishing orphan drug legislation. Japan is the second country who enforced orphan drug legislation in 1993. The orphan drug legislation is intended to address the inhibiting costs of product development and difficulties of limited profit potential related to a small market size for each rare disease. These legislations incorporate various incentives to encourage research, development and marketing of orphan drugs. These generally consist of tax credits for research costs of orphan drugs, marketing exclusivity of multiple years preventing authorization of a generic drug or brand name for the same rare disease indication, free scientific advice such as help on protocol, fast follow-up/priority review for marketing and pre-authorization off-label use [14-17].

Some countries have accelerated procedures to ensure on-time marketing of orphan drugs. These procedures are: Priority review, fast follow-up approval and accelerated approval. Although the process is applicable to both orphan and non-orphan drugs, despite the fact that it's accepted more for the orphan drugs, the orphan drugs are not appropriate for automatically accelerated procedures. In some countries, less stringent criteria are used in the assessment of the therapeutic value of orphan drugs. The criteria related to unfulfilled need, severity and high clinical efficacy must be met for accelerated review. For example, in USA, the priority review is ensured for orphan drugs demonstrating remarkable improvement in treatment or those fulfilling an important unfulfilled need. For instance, iloprost, an orphan drug for treatment of pulmonary arterial hypertension experienced priority review in the US in December 2004, with a positive outcome within 6 months as compared to the regular 10 month assessment period. An accelerated assessment usually takes about half the time needed for the standard marketing authorization process (~150 days versus a year or longer) [18-22].

Marketing authorization and pricing

Due to the inadequate literature, the pricing mechanism of orphan drugs is mostly defined as "black box" pricing. Because the research and development costs are collected from a few numbers of patients, the pricing of orphan drugs is unique. As a result of this marketing exclusivity and non-existence of therapeutic alternatives, orphan drugs are relatively expensive and their costs usually exceed 100,000 euro per year. (For example, the annual cost of Replagal, which is the drug used for the treatment of Fabry, a genetic X-linked lysosomal storage disease, is 265987.20 USD per patient.) Generally, there is not a remarkable difference in ex-factory (producer) costs of orphan drugs between countries with different pricing and reimbursement systems. Rather, the heterogeneity of prices and accessibility of orphan drugs between countries is likely to arise from budget restrictions and political pressures. The orphan drugs related to multiple indications, those for chronic treatments and those lead to the demonstration of improvement in life quality and survival are associated with higher annual prices. Repurposed orphan drugs, those administered orally and those for which alternative treatments are possible are associated with lower annual prices. The variability in accessibility and use of orphan drugs might be compared with the recently authorized non-orphan drugs in the EU [3, 18, 20, 23-25].

Marketing Authorization and Pricing Policies of Orphan Drugs in Turkey

In Turkey, the draft orphan drug guideline involves the conditions to be satisfied by the applicant in order a human medicinal product to be able to receive an orphan drug status. The orphan drug should be affecting 5 in 10,000 individuals at most, life critical or intended for diagnosis, prevention or treatment of diseases leading to chronic disability. In Turkey, it is required that the drug is intended for the diagnosis, prevention and treatment of diseases which are life threatening, causing serious disability or serious or chronic rare diseases and also that the research and development cost of the drug cannot be covered by the estimated sales figures without incentives. Besides, it is required that satisfactory methods for diagnosis, prevention and treatment of a certain disease do not exist and that, in case such a method exists, the drug to receive identification shall have a significant benefit for affected patients [14].

Once a submission has been made for marketing authorization of an orphan drug, TITCK requests information such as reliable and current references about the prevalence proving that it is 5/10,000 in Turkey or otherwise within the closest race and about the incidence, proofs showing that identification criteria are satisfied and comments about the development stage including targeted indications, studies/data related to prevalence and incidence of the disease if any, summary information about the activities and projects in EU or other countries and the financial supports if any, related scientific literature collection and the information in databases referring to such a collection if any, detailed documents related to grants, tax incentives or other cost gains in EU or other countries, studies/data proving that the introduction to market cost including the research and development cost of the orphan drug cannot be covered by predicted sales, justified declaration of the development costs likely to occur after submission, justified estimated figures related to sales revenues annually 6 years following the marketing authorization of the orphan drug in Turkey and on demand of the Institute afterwards [26].

Prior to the marketing authorization application in Turkey by the applicant for the identification of a human medicinal product as an orphan drug, application to the institution is possible at any stage of development. The institution might request additional information and documents from the applicant which are likely to include data related to the studies carried out in Turkey. The application file is subjected to a prior review in order to find out if there are missing information or documents. The review is made within 30 (thirty) days following the receipt of the application file by the institution and the situation is notified to the applicant. In case there are missing information or documents, the applicant completes them within 30 (thirty) days following the notification by the Institution. The second prior review to be made upon submission to the institution of the completed file is also concluded within 30 (thirty) days. The applications for which the missing items have not been completed and which do not fulfill requirements are rejected and returned to the owner. Upon receipt of a complete application, the institution assesses if the identification criteria are satisfied within 90 (ninety days). The assessment result about if or not the identification criteria have been satisfied is notified in written to the applicant within this 90 (ninety) days. If the assessment results as the application does not satisfy the identification criteria, its causes are expressed within the written notification. If the assessment results as the application satisfies the identification criteria, the orphan drug is added into the "The National List of Drugs Assigned to Orphan Status" published on the related internet page of the institution. The institution regularly reviews the list and updates it at least annually [26].

The marketing authorization process of the orphan drug identified by the institution and added in to "The National List of Drugs Assigned to Orphan Status" is carried out according to the provisions of the Regulation. The provisions of Regulation are applied to all application and marketing authorization process. The applicant reserves right to make another marketing authorization application for the indications out of the guideline. The applicant submits a current report about the development of the orphan drug annually [26].

For all applications of the human medicinal product designated as an orphan drug, 10% of the prices in the current price list are applied. The marketing authorization applications for the orphan drugs in "The National List of Drugs Assigned to Orphan Status" are carried out in parallel with the Good Manufacturing Practices inspection applications. During the marketing authorization process of the orphan drugs, high priority is ensured according to the decision of the Prioritization Committee. The prices of the orphan drugs are determined according to the related current provisions of the Notification on the Pricing of Human Medicinal Products published in the Official Gazette dated 11/12/2015 and numbered 29559 [26].

DISCUSSION AND CONCLUSION

It is predicted that the pharmacogenomics will lead to the designation of more orphan diseases in the future. Animal trials have shown that nuclear cloning, gen and cell therapy constitute exciting new strategies for the treatment of genetic diseases. Nuclear transfer of embryonic stem cells (derived from rat cumulus or fibroblast cells) can be transformed to somatic cells such as myogenic cells, dopaminergic and serotonergic neurons, hematopoietic cells or pancreas islet-like cells. Strategies such as therapeutic cloning might prove that there can be future of the treatment of neurodegenerative diseases and blood dyscrasia. Adult stem cells may help the treatment of some rare diseases. Ethical notions prevent the development of therapeutic cloning [27-29].

Applying to orphan drugs the new drug design technologies which are included within the drug investigation programs might lead to better results in a short time. The international support for orphan disease researches ensures encouragement and motivation for overcoming financial obstacles and encourage the development of the treatment in the world. Thus, the future promises hope for patients who have been neglected to date due to profit-driven drug investigation studies [27-29].

In Turkey, studies are carried out to determine needs and priorities. Orphan drugs are identified, lists are prepared and road maps are drawn. The health authority plans the establishment of a national register system for orphan diseases defined with a different code, construction of diagnosis and treatment centers and building networks among them and it also encourages multi-center clinical trials involving our country to improve cooperation within the country and with Europe [26].

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