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Orphan Drugs: Review Article

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Abstract

Drugs that have limited access and treat rare diseases are called "orphan drugs". These drugs are called "orphan" because the pharmaceutical industry has little interest in developing and marketing these drugs, which are used only for a few patient groups. This is because pharmaceutical companies cannot compensate the very high cost of developing these drugs. This review article aims to give information about orphan drugs, policies about these drugs and difficulties to reach them.

Keywords: orphan drugs, rare diseases, pharmaceutic, marketing

1. Definition

An "orphan drug" can be defined as a drug used to treat a rare disease. For example, heme arginate is an orphan drug used to treat acute intermittent porphyria, variegated porphyria, and hereditary coproporphyria (1). In addition, it is surprising that ibuprofen can also be classified as an orphan drug because it is used to treat a rare disease like patent ductus arteriosus in newborns. In some cases, even for a drug whose efficacy has been well established elsewhere, it may be of no commercial value to initiate an efficacy trial (2)

The definition of orphan drugs may vary from country to country and region to region. The definition of orphan drug in Türkiye is found in the "Communiqué on Pricing of Medicines for Human Use," which entered into force in the Official Gazette dated September 22, 2007, and numbered 26651. In this definition, orphan drug is defined as "drugs used in fully defined diseases with an incidence of affecting less than 100,000 people in a country" (3).

2. Methods

Keywords "drugs, orphan drugs, reimbursement, drug policies, market size of drugs" and combinations of these words were searched in health databases (PubMed, Embase, Google Scholar). Studies involving at least one subject for orphan drugs were included in the review. Orphan drugs were reviewed under these sections: importance, pricing and reimbursement, market size, current policies and difficulties experienced in accessing orphan drugs.

3. Importance

Whether a disease is rare or not, discovery, development, and clinical testing of a drug that can treat it are long, demanding, and expensive processes. For this reason, pharmaceutical companies avoid investing in a product for a disease that affects a relatively small number of people, which they believe cannot generate a return on their investment (4). This causes patients diagnosed with rare diseases to have difficulties accessing drugs.

4. Pricing and reimbursement of orphan drugs

The first Orphan Drug Law was enacted in the United States of America (USA) in 1983 in order to encourage the research and development of orphan drugs and their placing on the market, as well as to provide equal health care to patients suffering from rare diseases. Following this, the Pharmaceutical Products Law, which includes special conditions for the development of orphan drugs, was put into effect in Japan in 1993 and the Orphan Drug Regulation (EC 141/2000) in 2000 in the European Union. Later, legal regulations were put into practice in order to encourage the development of orphan drugs and increase Access (5).

Legal regulations and commercial incentives are provided to support long-term investments in rare diseases and to develop new treatments for patients in order to eliminate uncertainties and difficulties faced by orphan drug companies in research and development activities in the USA and Europe. The US Congress allocates an annual donation of approximately 20 million USD to the Food and Drug Administration (FDA) for orphan drugs. The European Union allocates significant rare disease funds under the FP7 and Horizon 2020 programs. In addition, the countries have additional national exemptions and incentives (6,7).

Following the regulation of the health system with legal regulations, the responsibility to strengthen and support the research activities carried out became widespread; the Cross-border Health Care Directive in the European Union (EU), the

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European Reference Network and a European Rare Diseases Group were established. In addition, national health systems in European Union member countries have created many rare disease-focused strategies and plans. Also, countries such as Russia, China and Australia have legal regulations that rapidly increase their orphan drug R&D capacities (7). Incentives provided in the development of orphan drugs in the USA, Japan and the EU are given in Table 1.

Table 1. Incentives provided in the development of orphan drugs

	USA	Japan	EU
Legal framework	Orphan Drug Act (1983)	Revised orphan drug regulations (1993)	Orphan drug regulation (Commission Regulation) (EC) No 141/2000 (1999)
R&D donations	Phase I-III Clinical Trials (USA 2008-2012, 30 million USD per year)	Clinical and non-clinical studies	Specific to the EU member countries
Tax advantages	50% of the R&D cost	15% tax deduction; corporate tax deduction up to 14%	Specific to the EU member countries
Quick and priority review	Available	Available	Available (EU central approval)
Protocol support	Available	Available	Available
Exemption or discount from application fees	Available	Available	Available
Market exclusivity	7 years	10 years	10 years (additional 2 years when approved pediatric research plan is completed)

While the annual R&D expenditure for orphan drugs across European Union countries was 158 million euros in 2000, it increased to 480 million euros in 2008 following the Orphan Medicines Regulation (EC 141/2000) (7). However, despite this, the share of rare diseases in total drug expenditures is 4-5%, and the share of ultra-rare diseases is around 0.7% (8-10). Despite all these incentives, only 5% of rare diseases have a treatment option that has been approved by the FDA for orphan drug status (7).

The main companies in the orphan drug market are: Bristol-Myers Squibb Company, Celgene Corporation, F. Hoffmann-La Roche Ltd., Amgen, Biogen, Bayer, Novartis AG, GlaxoSmithKline plc., Johnson & Johnson, AbbVie Inc., Eli Lilly and Company, Alexion Pharmaceuticals, Shire, Novo Nordisk, AstraZeneca, Eisai, Daiichi Sankyo, Merck, Teva Pharmaceutical Industries, Actelion Pharmaceuticals Ltd. and Aegerion Pharmaceuticals (11).

5. Market size of orphan drugs

The global orphan drug market is expected to reach 229.71 billion USD in 2026, with an increase of 10.4%. The increasing prevalence of rare diseases is a key factor driving the growth of the orphan drug market. Rare disease treatments often require a cold supply chain, which is not readily available in all countries. The main orphan drug types are divided into Biological and non-biological categories. Various treatments in oncology, hematology, neurology, endocrinology, cardiovascular and respiratory system diseases, and immunomodulators used for the treatment of oncology, hematology, neurology, cardiovascular and other diseases contain orphan drugs (11).

6. Current policies in our country for access to orphan drugs

Currently, there is no national orphan drug legislation in force in Türkiye. In 2008, the Orphan Drugs Operation and Evaluation Group was established under the Association of Research-Based Pharmaceutical Companies with the participation of 25 out of 39 members (Association for the Advancement of Pharmaceutical Awareness and Rational Drugs 2014). In 2011, the National Orphan Drug Guidelines Draft was prepared by the Turkish Medicines and Medical Devices Agency and shared with the sector representatives, and suggestions were received. In September 2014, at the "Rare Diseases and Orphan Drug Symposium and Orphan Drug Regulation Workshop" organized by the Drug Awareness and Rational Medicine Association, the Ministry of Health presented the draft guideline for the field view (12).

A 2016 study stated that 45 of the 86 orphan drugs licensed in the EU were reimbursed by the SSI (Social Security Institute). Fifteen of them were licensed in our country and included in the positive list (Annex 4/A), and the remaining 30 drugs are included in the foreign drug list (Annex 4/C) provided on behalf of the patient through the Turkish Pharmacists Association (TPA) (13).

In a study conducted in 2020, it was stated that 34 of the 105 rare drugs on the list of the European Medicines Agency can not be accessed from Türkiye. Among the 71 drugs available in Türkiye, 23 (32%) were licensed, while 48 (68%) were unlicensed. 17 (74%) of licensed products and 17 (35%) of unlicensed products were included in the scope of reimbursement. The same study showed that the most commonly used orphan drug group was "L-Antineoplastic and Immunomodulator" agents (14).

In addition, the practices in Türkiye where the pricing and reimbursement processes of orphan drugs can be differentiated from other drugs for human use are specified in the Law, Decision and Communiqué below, and similar procedures are applied to all drugs except for these exceptions;

Communiqué on Pricing of Medicinal Products for Human

Use (December 11, 2015)

Decision on Pricing of Medicinal Products for Human Use (February 24, 2017)

Social Insurance and General Health Insurance Law No. 5510 (June 16, 2006) (3).

There is a need for the implementation of incentives and support in national policies in order to enable companies to develop orphan drugs to increase their investments in Türkiye and offer their products rapidly to the Turkish market (7).

7. Difficulties experienced in accessing orphan drugs

Although no legislation envisages specific incentives for orphan drugs in Türkiye, some ways exist to enable access to orphan drugs. Thanks to these facilities, patients can access their treatments quickly and equally. Only with the publication of unique legislation will it be possible to introduce financial and regulatory incentives and encourage domestic production in this field.

The supply of orphan drugs in Türkiye is carried out in three different ways:

If it's licensed and already available for purchase

It may be unlicensed in Türkiye. However, on a per-patient basis, if approved in the US or EU, or if an efficacy safety study has been done.

Approved ones for early access to drug programs for clinical application to patients

Pursuant to the Regulation on Licensing of Medicinal Products for Human Use in Türkiye, the Ministry of Health completes the preliminary examination within 210 days from the date of application. If a drug complies with the legal regulations, its application gets finalized (15).

Orphan drugs, which are not allowed to be used for a specific indication in Turkey and are not licensed by TMMDA (Turkish Medicines and Medical Devices Agency), are delivered to patients in need through the early access procedure. This procedure allows physicians to prescribe these drugs. Physicians who want to prescribe off-label drugs should apply to TMMDA for patient approval. TMMDA evaluates each application according to published scientific evidence and recommendations of scientific committees. When the use of an off-label drug is approved by TMMDA, importation of that drug is provided by the Turkish Pharmacists Association (16).

Conflict of interest

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Authors' contributions

Concept: H.A., Design: H.A., Data Collection or Processing: H.A., Analysis or Interpretation: H.A., Literature Search: H.A., Writing: H.A.

Ethical Statement

This study does not require ethics committee approval.

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