T.C.
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PHARMACOEPIDEMIOLOGY

# RECENT ISSUES ON ACCESSIBILITY TO ORPHAN DRUGS AND POLICY IMPLICATIONS IN TURKEY

MASTER THESIS

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## APPROVAL

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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ...17.01.2020... and numbered .2020/01-51

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## DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Sibel ATALAY

**To my beloved family**

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| | |
|---|---|
| AIFD | Association of Research-Based Pharmaceutical Companies |
| ATC | The Anatomical Therapeutic Chemical |
| COMP | Committee for Orphan Medicinal Products |
| EMA | The European Medicines Agency |
| E-Rare-3 | The European Commission Programme, Rare Disease Research |
| EU | European Union |
| EC | European Commission |
| EUCERD | European Union Committee of Experts on Rare Diseases |
| FDA | Food and Drug Administration |
| HTA | Health Technology Assessment |
| ICD | International Classification of Diseases |
| IQVIA | IMS Health and Quintiles, Inc. |
| TMoH | Turkish Ministry of Health |
| NICE | National Institute of Clinical Excellence |
| R&D | Research & Development |
| SSI | Social Security Institution |
| TMMDA | Turkish Medicines and Medical Devices Agency |
| TPA | Turkish Pharmacists' Association |
| UK | United Kingdom |
| US | United States |
| WHO | World Health Organization |

## ABSTRACT

**Atalay, S. (2019). Recent Issues on Accessibility to Orphan Drugs and Policy Implications in Turkey. Yeditepe University, Institute of Health Science, Department of Pharmacoeconomics and Pharmacoepidemiology, MSc Thesis. İstanbul.**

Rare diseases are conditions which affects a small percentage of the population, life-threatening, serious genetic, chronic, complex and needed special care. It is estimated that one in 15 people worldwide can be affected by rare diseases. According to The U.S. Food and Drug Administration (U.S. FDA), diseases that are affecting less than 200.000 people are defined as rare diseases. It is estimated that rare diseases affecting not more than 1 person per 2000 in the EU population. Orphan drug is a type of medicine which is developed specially to treat a rare medical condition. It is very high cost to develop orphan drugs for patients in very small populations. Therefore, the government sector support is important to encourage pharmaceutical companies to develop orphan drugs. This study has been conducted to contribute to determining the deficiencies and development goals, and therefore, preparing action plans, by setting out the market access of the policies introduced on the Rare Diseases in Turkey and of orphan drugs used in the treatment of rare diseases in full detail. In Turkey, national regulations allow patients to access registered orphan drugs either through national reimbursement system of payer or through out of pocket payment contribution by patients. Non-registered orphan drugs can be accessible through national patient accessibility programs. Depending on the status of the non-registered orphan drug, either it might be reimbursed by the payer or it might be compensated by the patients. Based on The European Medicines Agency (EMA) publications, 105 pharmaceuticals are approved with orphan drug status by December 2018. Among approved 105 EMA orphan drugs, 36 of them are not available in Turkey, only 69 of them are accessible. 32 out of 69 accessible orphan drugs are licensed products by Turkish Ministry of Health. Among 32 licensed orphan drugs, only 26 of them are reimbursed by national payer. Within 69 accessible orphan drugs, 37 of them are at the non-registered product status and only 19 out of 37 are reimbursed through national payer. The rest of these reimbursed drugs could only be compensated by patients. It is estimated that in Turkey, orphan drugs have 276 million € sales in 2018. It is very important to have

an orphan drug incentive policy in order to ensure early access to drugs used in rare diseases. First it must prepare a regulation on orphan drugs with Turkey.

**Key words:** Orphan drug, access to drug, orphan drug policy, rare diseases.

# ÖZET

**Atalay, S. (2019). Türkiye'de Yetim İlaçlara Erişilebilirlik ve Yetim İlaç Politikasına İlişkin Güncel Durum. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Farmakoekonomi ve Farmakoepidemiyoloji ABD., Master Tezi. İstanbul.**

Nadir hastalıklar; popülasyonun küçük bir yüzdesini etkileyen, yaşamı tehdit edici ciddi genetik, kronik, karmaşık ve özel bakım gerektiren hastalıklardır. Dünya çapında her 15 kişiden birinin nadir hastalıklardan etkilenebileceği tahmin edilmektedir. Amerikan Gıda ve İlaç Dairesine (U.S. FDA) göre 200.000'den az kişiyi etkileyen hastalıklar nadir hastalıklar olarak tanımlanmaktadır. Avrupa Birliğinde ise nadir hastalıkların her 2000'de en fazla 1 kişiyi etkilediği tahmin edilmektedir. Nadir hastalık olarak tanımlanmış bu gibi tıbbi durumları tedavi etmek için özel olarak geliştirilmiş ilaçlar yetim ilaç olarak adlandırılmaktadır. Çok düşük sayıdaki hasta popülasyonları için ilaç geliştirmek oldukça maliyetlidir. Bu nedenle ilaç şirketlerinin yetim ilacın geliştirilmesinde teşvik edilmesi için kamu sektörünün desteği gereklidir. Bu çalışma ile Türkiye de Nadir Hastalıklar ile ilgili oluşturulan politikaların ve Nadir hastalıkların tedavisinde kullanılan yetim ilaçların pazara erişim durumunu tüm detaylarıyla ortaya koyarak, eksiklikler ve gelişim hedefleri ve bu doğrultuda aksiyon planlarının belirlenmesinde katkı sağlanması amaçlanmıştır. Türkiye'de ulusal düzenlemeler, hastaların ruhsatlı yetim ilaçlara ulusal geri ödeme sistemi aracılığıyla veya hastaların kendilerinin ödemesiyle erişmelerine izin vermektedir. Ruhsatlı olmayan yetim ilaçlara, ulusal hasta erişilebilirlik programları aracılığıyla erişilebilmektedir. Ruhsatlı olmayan yetim ilacın durumuna bağlı olarak, ilaç ya geri ödeme kapsamında ödenebilmektedir ya da hasta tarafından karşılanabilmektedir. Avrupa İlaç Ajansı (EMA) yayınlarına göre, Aralık 2018 itibariyle 105 ilaç yetim ilaç statüsü ile onaylanmıştır. EMA'da onaylı 105 yetim ilaç arasından 36 tanesi Türkiye'de mevcut değildir, yalnızca 69 tanesi erişilebilir durumdadır. Erişilebilir 69 yetim ilaç içerisinden 32 tanesi TC Sağlık Bakanlığından ruhsatlı ürünlerdir. Ruhsatlı 32 adet yetim ilaç arasından sadece 26 tanesi ulusal ödeme sistemi yoluyla geri ödenmektedir. Ruhsatsız ürün statüsünde olan 37 ilaçtan ise sadece 19 tanesi ulusal ödeme sistemi yoluyla geri ödenmektedir. Geri kalanına yalnızca hasta tarafından ödenmesi yoluyla erişilebilmektedir. Türkiye'de yetim ilaçların 2018 yılında 276 milyon Avro satış yaptığı tahmin edilmektedir. Nadir hastalıklarda kullanılan ilaçlara erken erişim sağlamak için

yetim ilaç teşvik politikasına sahip olmak çok önemlidir. Bunun için öncelikle, Türkiye'de yetim ilaçlar konusunda yasal bir düzenleme hazırlanması gerekmektedir.

**Anahtar Kelimeler:** Yetim ilaç, ilaç erişimi, yetim ilaç politikası, nadir hastalıklar.

# 1. INTRODUCTION and PURPOSE

Human beings interact with each other by nature, and this is the way they maintain their lives. Health problems affect humans physiologically, psychologically, socially and economically, and they can prevent humans from maintaining a functional life (1).

There has been a lack of awareness of rare diseases and orphan drugs, which makes the area an unknown field. Other countries also esteem this field a privilege and approach it with various regulations. Rare diseases are by definition not only rare in a society but also create a social health problem by threatening life or causing serious disability, and diseases which have a prevalence of five per ten thousand in a society. Decreased quality of life and efficiency, continuous hospital visits, the feelings of dependency, being a burden and depression also reflect on patient's relatives and affect the patients negatively. Especially families of the patients who suffer from a rare disease are affected seriously in almost every process from diagnosis to treatment.

Many countries therefore implement regulations promoting the development of orphan drugs. Orphan drugs which are used in the treatment of rare diseases could only be brought forward in 1980 in the US, in 1993 in Japan, in 1998 in Australia and in 2000 in the EU, and began to be considered differently than other diseases. In Turkey, this issue has been dealt with as from 2011 and Turkish Medicines and Medical Devices Agency (TMMDA) prepared the National Draft Guidance on Orphan Drugs. Furthermore, it was decided to "build capacity for orphan drugs in Turkey" and the Ministry of Health was appointed for this task under the Action Plan of Structural Transformation Program for Healthcare Industries which was created as part of the 10th Five Year Development Plan published in 2014. In other words, the view of developing various policies for patients who fight against rare diseases has been adopted by the public in the last few years and several objectives have been set, taking the opinion and suggestion of all the stakeholders in the field of rare diseases and orphan drugs. In this context, the purpose of this study is to contribute to determining the deficiencies and development goals, and therefore, preparing action plans, by setting out the market access of the policies introduced on the Rare Diseases in Turkey and of orphan drugs which are used in the treatment of rare diseases in full detail.

Rare diseases are not widely known and occur in extraordinary ways and typically with comorbidities, which makes their diagnosis more difficult. On the other hand, there is neither method nor facilities to diagnose many rare diseases. Besides, the number of

doctors who can diagnose and cure rare diseases is very limited. For this reason, it is really difficult to find the appropriate treatment and patients may spend many years full of uncertainty (2,3).

One of the problems that is encountered for rare diseases is that Research and Development (R&D) is not desired. Furthermore, the number of clinical and preclinical scientists, policy makers, industry professionals and academicians in this field is insufficient (2).

Another problem which is faced with in the case of rare diseases is invisibility of the burden caused by these diseases to the health system because of misclassification and inappropriate coding (4).

# 2. LITERATURE REVIEW

## 2.1. Rare Diseases

Rare diseases are serious genetic (5), chronic (6) and complex (2) diseases with a low prevalence that are life-threatening and require care (7). Rare diseases, other than the ones which are genetic in origin, are cancers, autoimmune diseases, or degenerative and proliferative diseases, or caused by infections and infestations (5).

Although the definition of rare diseases may vary (2,5,8), in the US it is defined as diseases which affect fewer than 200,000 individual, 50,000 in Japan and 2,000 in Australia (6,8). In summary, the prevalence of rare diseases mainly vary from about 1 to 8 in 10,000 (8). According to the report issued by World Health Organization (WHO) in 2013, a disease is called rare disease if less than 5 people per 10,000 is affected (6). Epidemiological data have been changing worldwide constantly. Today, a disease which is considered to be rare may become epidemic/common in the future. Moreover, in every week new rare diseases are discovered and many of them do not have any treatments available (5).

Yet Ultra Rare Diseases has a different definition under the rare diseases' categories, there is not any specific official definition for them. However, the UK's National Institute of Clinical Excellence (NICE) defines this term as affecting less than 1000 people in England and Wales (9). Since there is no general definition on ultra rare diseases, analyses and comments in this respect are made based on this definition.

Rare diseases may vary depending on time and geographical regions (10) because a rare disease in a country may be relatively less rare in other countries. For instance, cystic fibrosis which is one of a genetic disease, is rare in Asia while it is more common in Europe. Likewise, many contagious diseases are rare in developed countries while their prevalence is higher in less developed countries. Among Finnish population, there are 40 rare diseases with a high prevalence (5).

**Table 1:** Definitions of Rare Diseases According to Member States of the European Union*

| | |
|---|---|
| Sweden | Diseases or disorders results in an extensive disability which has a prevalence of less than 100 in 1 million individuals. |
| Finland | Serious or debilitating diseases affecting 1 in 2,000 individuals. |
| Denmark | There is no official definition. Health authorities of Denmark tend to define rare diseases as diseases affecting 500 - 1,000 people in the Danish population. |
| Estonia | There is no official definition. Definition of the European Union has been accepted. |
| Belgium | Life-threatening or chronically debilitating diseases with a prevalence of less than 5 per 10,000 individuals affected by these disease which is needed special combined care. |

*European Commission, 2014.

These diseases which affect the patient's life quality and life expectancy negatively manifest themselves in serious mental and physical disorders. They have different epidemiological characteristics depending on country and they pose a major health problem across society. Therefore, rare diseases which involve difficulties in diagnosis, treatment and follow-up, require different approaches compared to other diseases (11).

In spite of the fact that each of the rare diseases affect only a few number of patients, it is estimated that there are 8,000 - 10,000 rare diseases in total. About 300 of these diseases can be treated with approved medicines. In other words, there is no appropriate treatment for about 95% of rare diseases. Children are affected 75% of rare diseases. 30% of the affected children pass away before 5 years old (12).

There is a therapeutic disparity between the number of known rare diseases and diseases which have an approved treatment. These means that there is the severe unmet medical need for most of rare diseases (13).

The great majority estimated as 80% of rare diseases are genetic in origin (13). The total number of rare diseases with genetic basis vary between 6,000 and 8,000. When all rare diseases are considered, although each one affects few patients, in fact, from 6% to 10% of the general population are thought to be affected from rare diseases (6). It is very roughly estimated that one out of 15 people worldwide could be affected by a rare

disease where 400 million people worldwide, of whom 30 million are in Europe and 25 million in the United States (US) (6).

### 2.2. Orphan Drugs

'Orphan' as a word is originated from the Greek word *orphanos*. It means the child who lost their one or two parents by death or the adult who lost their children by death. The obsolete English words, "orbation" and "orbity", mean orphan or childless (8).

In medical sense, the word 'orphan' first used in 1954 by Melnick. It is used for new viruses, provisionally called "orphan viruses" which is known so little to what diseases they belong. These viruses found in the patients whom suspected of having nonparalytic poliomyelitis (8).

Orphan drug is a type of drug which is developed specially. They are used for treatment of a medical condition which is rare. Developing drugs for patients with very small populations requires high cost. Therefore it is critical involving of government sector to the orphan drug market for rare diseases. The government sector support is also important since pharmaceutical companies which could study on rare diseases and develop orphan drug are not encouraged in the current situation (14).

For instance, companies such as Genzyme which was purchased by Sanofi-Aventis in 2011, focus on efforts to develop treatments for rare diseases, and they continue their business lucratively. Genzyme offers two products for Pompe disease. Myozyme and Lumizyme are approved as orphan drug by the US FDA in 2006 and 2010 respectively. These drugs have significantly improved the survival rate of patients who are suffering from Pompe disease, affecting 5,000-10,000 people worldwide (1 in every 40,000 people in the US and Netherlands, 1 in every 145,000 people in Australia, and 1 in every 600,000 in Portugal) (14).

For pharmaceutical companies it is not priority developing an orphan drugs to treat rare diseases as it is difficult to achieve a favorable return on R&D investment. For this reason, all stakeholders such as regulators, pharmaceutical industry, researchers and physicians should working on exploring the innovative ways to achieve a treatment of rare diseases which is effective, fast, affordable and successful for patients (13).

Despite all these constraints, in recent years, researches conducted in medicine on rare diseases has been increasing rapidly. This is because the US, which constitutes the half of world market, has taken significant steps in this field. In a research conducted in

2013, it was reported that in the clinical research process there were 5400 new molecule entities and totally 1795 projects related rare diseases are in the development process. These researches are expected to increase in the upcoming years. The companies related small molecule and biotechnology lead the most significant part of the researches on development of orphan drugs for patients suffering from rare diseases (15). The sense of "high quality healthcare" in the developing countries is becoming an increasing priority. Therefore, an interest in orphan drugs for rare diseases and potential treatments is increasing day by day in these countries (14, 16).

It is important to establish an incentive policy on orphan drugs (market exclusivity) in order to provide patients in Turkey with early access to innovative drugs used for rare diseases. 'Orphan drug' must be defined in order to provide patients suffering from rare diseases with quick access in Turkey. Additionally, maintaining the sustainability of companies which operate in the area of rare diseases and encouraging investments in rare diseases of Turkey are of importance. For this reason, defining the period for market exclusivity is a major step to ensure that patients suffering from rare diseases access orphan drugs uninterruptedly (17).

### 2.3. Orphan Drug Market

Obtaining the marketing authorization for a drug does not mean that it is available in all countries of the European Union (EU). Marketing authorization holder should first decide on commercialization situation in each country. Then, required procedures are followed for the drug in order to determine the its price and reimbursement conditions (18).

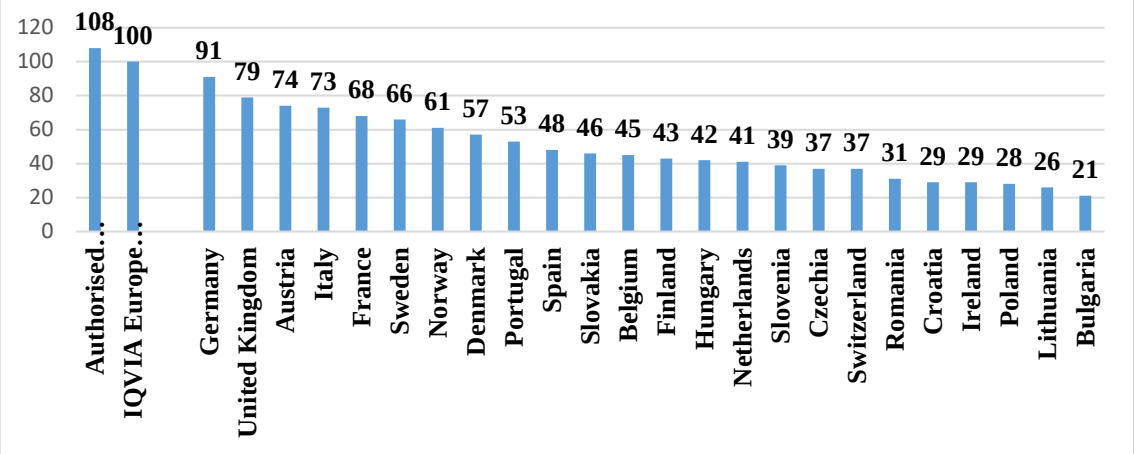


**Figure 1:** Scope of Orphan Drugs across Europe according to 2018 IQVIA data (19)

Figure 1 shows the total amount of authorized orphan drugs, the number of orphan drugs determined as part of IQVIA Europe and the number of orphan drugs available in European countries. There are 8 authorized orphan drugs which are not available across Europe because of either cell/gene therapies or recent approvals. Germany is the country where the largest range of orphan drugs is available (19).

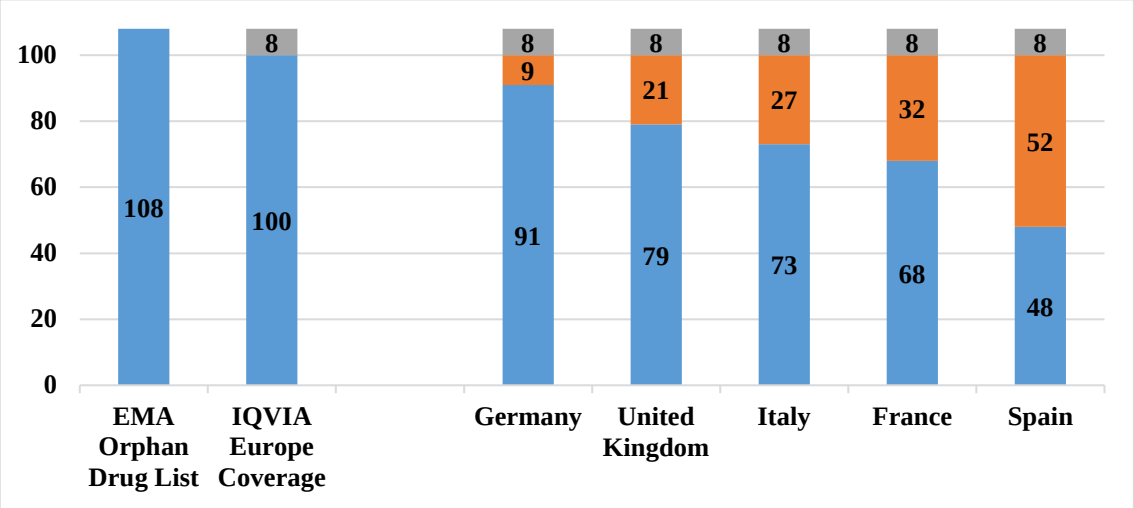


**Figure 2:** Scope of Orphan Drugs in 5 Big Countries of Europe according to 2018 IQVIA data (19)

8 products shown in grey color in Figure 2 are not found in any European countries. 8 out of 9 products in Germany, 16 out of 21 products in the UK, 24 out of 27 products in Italy, 29 out of 32 products in France, 50 out of 52 products in Spain cannot be found locally. Remaining products comprise of drugs concerning cell and gene therapy (19).

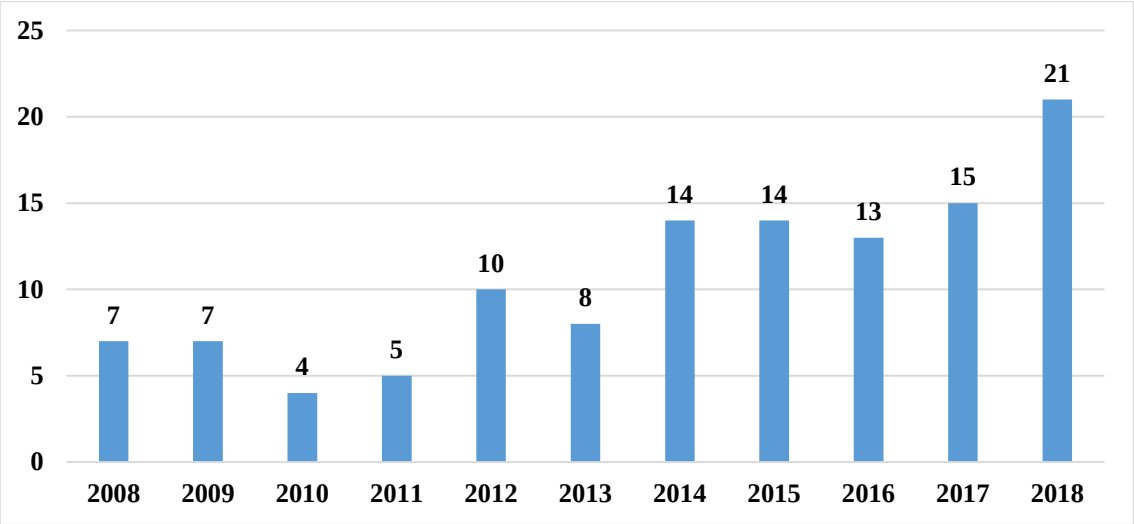


**Figure 3:** Number of Orphan Drugs Granted Market Authorization by EMA between 2008-2018 (19)

Figure 3 shows the number of orphan drugs with market authorization given by EMA. In recent years, an increase has been observed in the authorization of orphan drugs (19).

Despite having a small market share, orphan drugs contribute to the growth in European market to a large extent. Orphan drugs growing 29.1% in Europe in 2018 has contributed to the 8.7-billion-Euro increase in expenditure in Europe. Orphan drugs constitute 5% of the general pharmaceutical budget. Share of orphan drugs in total sales of pharmaceuticals in Austria, Germany, the UK, Denmark, and Slovenia is more than 6% (19).

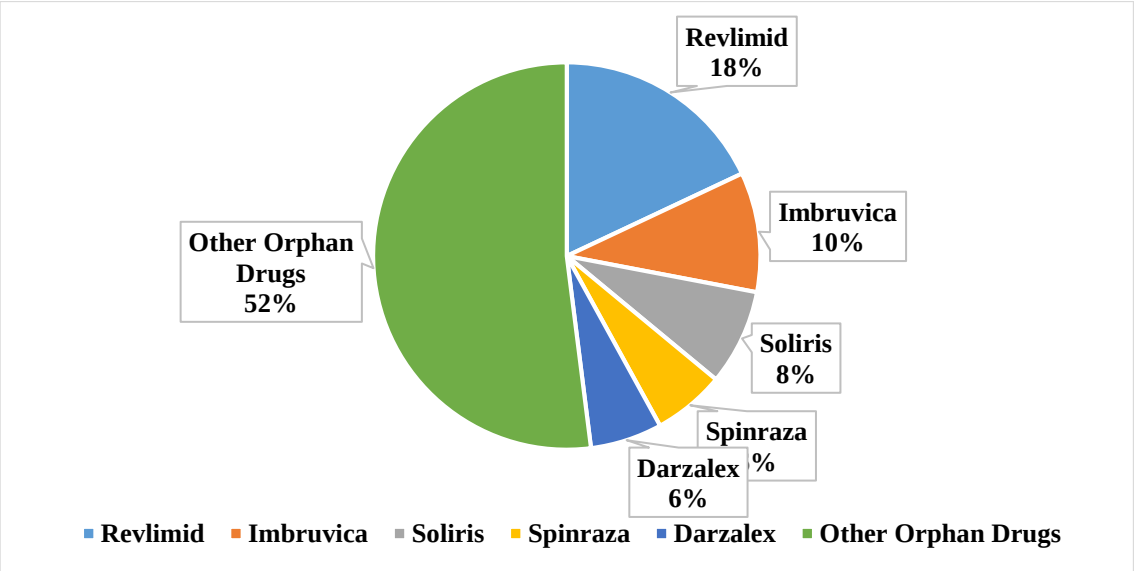


**Figure 4:** 5 Products Having the Biggest Share of Orphan Drug Market in Europe in 2018 (19)

5 products shown in Figure 4 comprise 48% of European orphan drug market in 2018 and contribute to market growth by 62% (19).

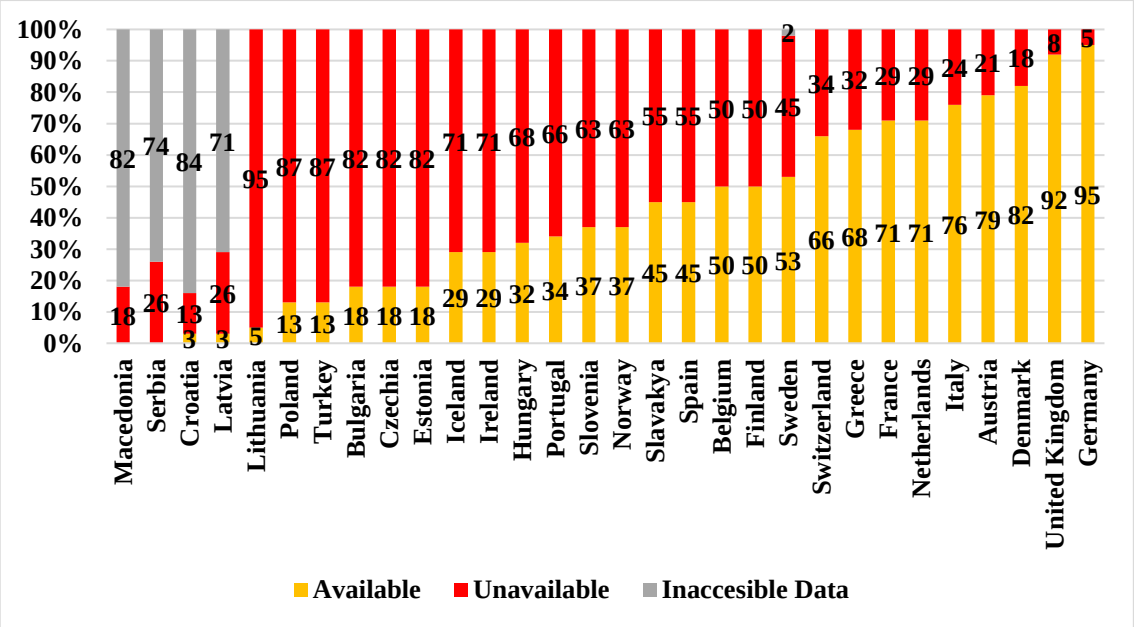


**Figure 5:** Availability rate measured based on the number of current pharmaceuticals as of 2018 (19)

For most countries, an orphan drug's availability means its inclusion in the reimbursement list. In Figure 5, the number of orphan drugs which are available or unavailable in European market is compared (19).

### 2.4. Marketing Authorization of Orphan Drugs

There are policies developed by the governments for R&D and marketing processes of drugs which need to be produced to treat rare diseases, considering each country's population affected by those diseases. The purpose of these policies is, first, to encourage manufacturing companies to study in the relevant area and to develop a marketing process which will enable patients to reach orphan drugs. As a result, considering the affected population, it is not even possible for orphan drugs not to be included in the agenda of developed countries (11).

The Orphan Drug Act has been adopted in the US in 1983 to facilitate research, development and commercialization of the orphan drugs used for to treat rare diseases which are ignored to a great extent. Legislation and policy on orphan drugs have been successful in promoting the progression of improved treatments for rare diseases. Since these policies were implemented, more orphan drugs have been authorized to treat rare diseases in the US. Although there has been an obvious increase in the number of orphan drugs marketed with the enforcement of the Orphan Drug Act, it is not clear whether this increase is entirely due to the law or the influence of other forces such as patent expiration, the lack of innovative treatments, the growth of the biotechnology industry and molecular biology, increasing rare disease patient groups' and social media's efficiency (20-22).

There are certain challenges in market access of orphan drugs during the process starting from the approval of the European Medicines Agency (EMA) to reimbursement, including delays. In some European countries, reimbursement of orphan drugs still takes longer when compared to other medicines. Its primary reason is that, unlike the US, there are processes of Health Technology Assessment (HTA) in European countries.

HTA analyzes medicines, medical devices, surgical procedures and health care systems in terms of medical, social, economic and ethical aspects. For instance; HTA is conducted on new drugs when they are launched to the market. HTA makes price-benefit analysis and according to the results of these analysis they support pricing and reimbursement. HTA contributes to finding answers to the questions of decision makers in studies and organizations related to health policies and practices. Many developed

countries, particularly Canada, Australia, the UK, Germany, France, the Netherlands, Belgium and Sweden, apply the HTA in particular in making reimbursement decisions and determining reimbursement lists.

A limited number of HTA are performed on orphan drugs and generally result in negatively (19). When standard HTA procedures are applied to orphan drugs, these drugs will not be available as "cost-effective". The fact that companies devote their resources to the development of orphan drug to treat rare diseases means that there are less resources left for the treatment of common conditions. While it is clear that orphan drugs will have negative results according to HTA criteria, companies will not want to develop such drugs if they do not receive any incentives (23).

When HTA is carried out for orphan drugs, they often fail to meet standard cost-effectiveness criteria due to their high acquisition costs and clinical uncertainties. Therefore, HTA is not recommended for reimbursement decisions in European countries (24).

Orphan drugs can be marketed in all Member States of the EU when they are approved by EMA. However, presence and reimbursement is subject to review by the relevant national authorities. Committee for Orphan Medicinal Products (COMP) is responsible for reviewing designation applications (25).

In a study covering the period from August 2000 to December 2004, it has been observed that only 18 drugs (7.1%) were approved out of 255 orphan drugs in Europe. In the same period, out of 193 applications submitted to the EMA, 153 (79.3%) drugs were authorized (25).

### 2.5. Activities of Member States of the European Union Regarding Rare Diseases

Several countries and regions that understand the importance of high-quality healthcare and being aware of the necessity of alternatives to treat rare diseases appropriately have taken legal measures to develop orphan drugs and to increase market share of these drugs. After the first Orphan Drug Act of the US in 1983 some other countries such as Singapore, Japan, Australia adopted their orphan legislation. EU adopted their orphan legislation in 2000. In Turkey there is not a national legal measure about orphan drugs to treatment rare diseases (26).

Member States of the EU are using the International Classification of Diseases. The systems of this classification ICD-9 and ICD-10 does not cover most of the rare

diseases. In the recent time a number of the Member States have decided to put ORPHA codes (rare diseases codification system developed based on Orphanet data) into effect in parallel to the ICD nomenclature. The Joint Action of The European Union Committee of Experts on Rare Diseases (EUCERD) and WHO provide data for the ICD-11 draft to indicate the rare diseases in international nomenclatures (3).

The European Commission (EC) is supporting the Orphanet Joint Action with all associated and collaborating member states and the EU Health Programme for the reason collecting information about rare diseases. Orphanet is a relational database intended to link information about more than over 6,000 diseases. It is available in 7 languages and it is possible to make multiple queries. Also, for every country there are entry pages which can be used in national language (3).

The EC "White Paper, Together for Health: A Strategic Approach for the EU 2008-2013" has been adopted by the EC on 23 October 2007 to develop the EU health strategy, and rare diseases were identified as a priority (27).

A "Committee of Experts" on rare diseases has been established in the EU. This Committee considers the interest of public. One of the purposes of this Committee is providing implementation of activities of Community on rare diseases. Moreover the Committee encourages the Member States on sharing their experiences, policies and practices about rare diseases. The Committee assists the Commission in international cooperation on issues related with rare diseases (27).

The European Commission Programme, E-Rare-3 (Rare Disease Research) which supports research on rare diseases, called for proposals under the 2016 title "Clinical research for new therapeutic uses of already existing molecules (repurposing) in rare diseases". The call for clinical/preclinical researches for discovery of new rare disease treatments and/or repositioning of current proven rare disease treatments was responded by 25 institutes from 17 countries. As a result of these developments, applications for clinical research on orphan drugs have increased (28).

### 2.6. Incentives for Orphan Drug Development in the European Union

The EU is providing incentives for companies researching and developing pharmaceuticals for rare diseases if they cannot be developed in another way. Companies can make application to attain these incentives for drugs provided that they meet certain criteria (29).

All around the world countries have recognized that it is necessary adoption laws and regulations for incentives in order to develop new and innovative technologies in the field on orphan drugs for treatment of rare diseases (29).

In Europe countries, pricing and reimbursement policies are different from each other. It causes that accession and utilization of orphan drugs varies in regard to countries. As a result of this, inequity occurs between patients (30).

In the EU countries, orphan drugs have an advantage of marketing exclusivity after marketing authorization. Marketing exclusivity means that other companies are not allowed to market a drug for the same indication in the period of exclusivity. This exclusivity gives market power to the first manufacturer (30). The market is getting stronger as many orphan drugs do not have an alternative health technology (31).

Financial benefits and incentives provided by the EU are as follow (34):

- annual grants to cover the cost of clinical testing;
- tax deduction for clinical research costs;
- supporting clinical research studies; and
- market exclusivity to the approved orphan drug for several years

Following the success of the Orphan Drug Act in the US, the EU has adopted the 'Regulation on Orphan Medicinal Products' in April 2000 to support the treatment of patients suffering from rare diseases. Orphan medicinal products refer to the products involving diagnosis, prevention and treatment. During the 6 years as from orphan drug legislation was adopted in Europe, the EC has given grant for 442 orphan medicinal products and approved marketing for 31 orphan drugs among them. By the end of 2008, 569 products were given grant and 48 orphan drugs were authorized for marketing (11).

### 2.7. Rare Diseases and Orphan Drugs in Turkey

Problems experienced worldwide regarding rare diseases are inevitably occurring in Turkey as well. Turkey is a country where rare diseases already occur due to disease burden, consanguineous marriage and presence of various ethnicities (18). Insufficient number of specialist physicians, inadequate knowledge and experience on rare diseases, and expensive treatments are among the leading problems. Despite the fact that there are many researchers in Turkey who conduct studies on rare diseases, the number of researchers who reach a solution to those problems is very low due to the absence of

relevant regulations. When appropriate regulations are introduced for rare diseases and orphan drugs, taking more concrete steps towards diagnosis, treatment and prevention of diseases will get easier for both researchers/doctors and patients (26).

According to the Ministry of Health's Communiqué regard to Pricing of Pharmaceuticals for Human Use (2007), orphan drugs are designed to treat rare diseases and these diseases affect no more than 100,000 inhabitants in Turkey. When it is compared, rare disease prevalence of Turkey is significantly lower than the rate in the US and the EU. As a result of that, rare disease definition of Turkey, actually refers to ultra rare diseases' definition. It corresponds to a prevalence of roughly 0.1–9% per 100,000 people in a specific region (26).

Generally, in Turkey, reference pricing policy applies to the drugs. The prices of orphan drugs are determined according to the reference prices in the countries to which they are exported and manufactured. The prices of these drugs are updated annually based on the annual sales volume (26).

In Turkey detailed and currently ongoing studies about orphan legislation have been carried out by TMMDA since 2010. As a Result of these studies Draft Guidance document (not publicly issued) is prepared. One of the main purpose of this Draft Guidance is to promote researches about treatment for rare diseases and development appropriate treatment alternatives. The other purpose is to provide placement of these treatments and drugs on the market. Another purpose is determination orphan drugs criteria and authorization requirements (26).

There is no effective regulation on orphan drugs in Turkey. Yet, "Symposium on Rare Diseases and Orphan Drugs and Workshop on Orphan Drug Regulations" was held by İlaç Bilincini Geliştirme ve Akılcı İlaç Derneği (Drug Awareness and Rational Drug Association) between 13&14 September 2014 in Antalya. At the end of this workshop, a draft document of orphan drug regulation was introduced (11).

The publication of a unique legislation in this field is important so that financial and regulatory incentives could be applied. Also, orphan legislation provides increasing study of clinical researches with orphan drugs, reach of these drugs to patients easier and shortly. Moreover, it provides increasing of domestic manufacturing (26).

In Turkey, orphan drug processes are followed by TMMDA in three ways (26). A drug may be:

1. Licensed or on the market for sale;

2. Accessed on a case-by-case prescription approval, even if not authorized in Turkey, provided that its efficacy and safety are verified in the US or the EU, and a clinical trial protocol is running;

3. Be approved as part of a compassionate use programme which to be applied on patients.

Even though no orphan drug legislation has been introduced in Turkey, pricing and reimbursement policies aimed at certain groups of medicines are currently implemented. There are also no incentives for orphan drug development in Turkey. But, there are some nuncupative procedures in order to facilitate access to orphan drugs (33). However, these procedures are not sufficient for patient access to the therapy fast and equally.

In Turkey, under the Regulation on the Licensing of Human Medicinal Products, the Ministry of Health completes preliminary investigation within 210 days following the application. If the drug is in compliance with legislative regulations, its application is finalized. In the same Regulation, it is also stated that licenses can be issued for the orphan drug under certain conditions such as rarely seen indications of the drug if absolute evidence for sufficient efficacy and safety cannot be provided (33).

Following the initiatives in 2010 and 2014, legislation for orphan drugs was called for during the sectorial consultation meeting of TMMDA held in 7 March 2016. Turkish Pharmaceutical Sector Strategic Document and Action Plan (2015-2018) is a major step towards introducing legislation aiming at quicker accession to drugs used in the treating rare diseases. Accordingly, EMA and FDA legislation has been harmonized and remarks of Association of Research-Based Pharmaceutical Companies (AIFD) localized based on relevant regulations of our country have been forwarded to the Agency (17).

# 3. MATERIALS and METHODS

Access to orphan drugs which are protected worldwide, in the US and the EU in particular, with several different policies may vary from country to country. In Turkey, there is no legislation specific to rare diseases or orphan drugs, and this may be considered as a cause for access problems. However, no sufficient study has been conducted to confirm that.

In this study, current situation and needs analysis regarding the rare diseases in Turkey will be made. In line with the study results, orphan drug policy will be evaluated and access to orphan drugs will be reported.

## 3.1. Data Set

Literature review was conducted by searching the keywords of "nadir hastalık" (rare disease), "yetim ilaç" (orphan drug), "rare disease" and "orphan drugs" on databases of Google Scholar, Google Books, National Thesis Center, Proquest and Orphanet.

In addition to literature review, list of drugs required to carry out the analyses were accessed on the official websites of EMA, TMMDA, Social Security Institution (SSI) and AIFD.

For the data on public cost and consumption, official websites of TMMDA and SSI were used:

- SSI: http://www.sgk.gov.tr/wps/portal/sgk/tr
- TMMDA: https://www.titck.gov.tr/
- AIFD:https://www.aifd.org.tr/

IMS Health and Quintiles, Inc. (IQVIA) data set was used to access data on consumption in Turkey.

## 3.2. Data Analysis

Compiled data were transferred into Windows Office Excel Software. Transferred data were analyzed with certain identifiers. Those identifiers are:

- Authorization and access status of orphan drugs in Turkey
- Reimbursement status of orphan drugs accessible in Turkey

- Distribution of orphan drugs according to The Anatomical Therapeutic Chemical (ATC) codes
- Authorization and access status of orphan drugs according to ATC codes
- Reimbursement status of orphan drugs according to ATC codes
- Annual number of boxes, price and budget amount of orphan drugs
- Annual number of boxes, prices and budgets of orphan drugs according to ATC codes

### 3.3 Methods

At first, list of available orphan drugs in Turkey is specified. Secondly, 3 years cost between 2016 and 2018 of these specified orphan drugs to main payer is examined and upon this data current financial situation concerning orphan drugs in Turkey is analyzed.

## 4. RESULTS

A protocol was concluded between the Turkish Ministry of Health (TMoH) and Turkish Pharmacists' Association (TPA) for procurement of unauthorized or unavailable drugs in Turkey from abroad and, within the framework of this protocol, Units of Pharmaceutical Procurement from Abroad which acts as an economic enterprise within the body of TPA, was founded. Headquarters of these units is located in Ankara, and there are also branches of these units in Istanbul, Izmir and Ankara. In the event of a request for pharmaceuticals which are used for treatment of certain rare diseases and cannot be reached in Turkey, they are procured from abroad through these units and delivered to patients and patient relatives. Like TPA, Pharmaceutical Warehouse of İbn-i Sina Centre for Health and Social Security which is within the body of SSI also procures pharmaceuticals from abroad.

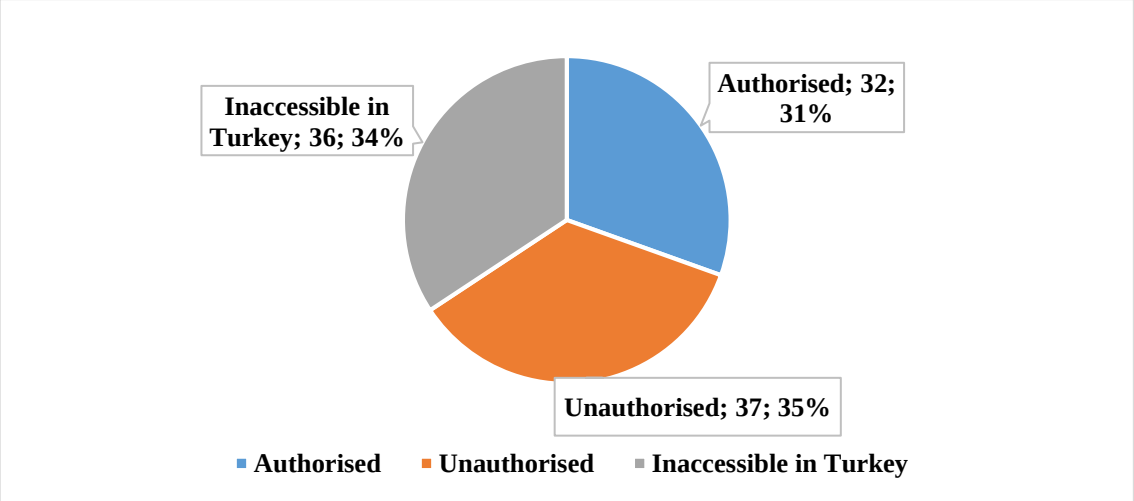


**Figure 6:** Authorization and Access Status of Orphan Drugs in Turkey

As it is shown in Figure 6, out of 105 products on the list of orphan drugs, 32 products (31%) are authorized and 37 products (35%) are unauthorized. The remaining 36 products (34%) are not accessible in Turkey.

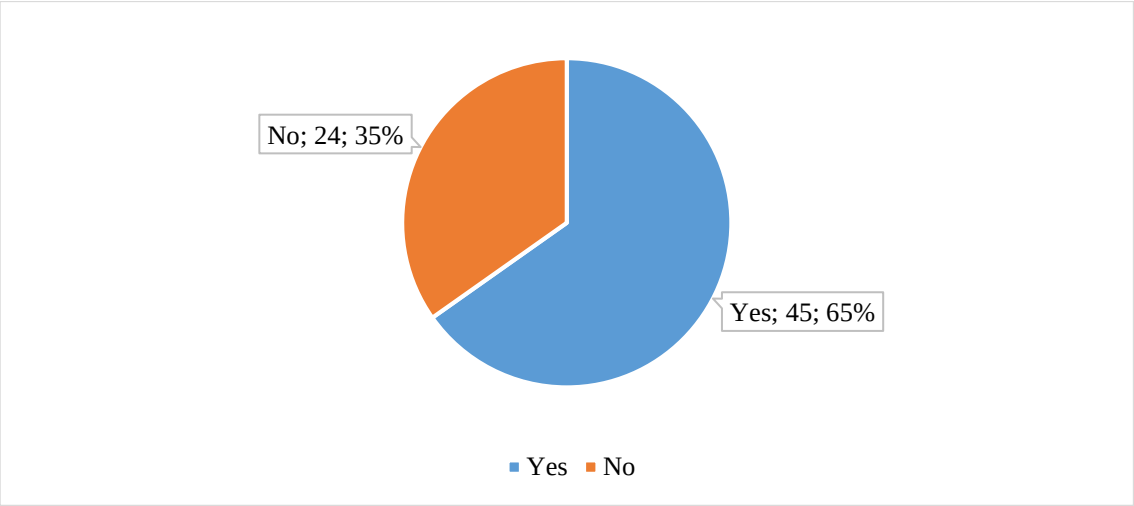


**Figure 7:** Reimbursement Status of Orphan Drugs Accessible in Turkey

Reimbursement status of orphan drugs which are accessible in Turkey is shown in Figure 7. When analyzed accessible orphan drugs in Turkey, it has been observed that 65% of them are under reimbursement.

**Table 2:** ATC Codes and Descriptions

| **ATC Codes** | |
|---|---|
| **L** | Antineoplastic and Immunomodulating Agents |
| **J** | Antiinfectives for Systemic Use |
| **B** | Blood and Blood Forming Organs |
| **M** | Musculo-Skeletal System |
| **N** | Nervous System |
| **V** | Various |
| **D** | Dermatologicals |
| **R** | Respiratory System |
| **C** | Cardiovascular System |
| **S** | Sensory Organs |
| **H** | Systemic Hormonal Preparations (Excl. Sex Hormones and Insulins) |

ATC codes and their descriptions are given in Table 2. ATC coding system is a system which provides international codification and classification of all the molecules that can be authorized and used as pharmaceuticals.

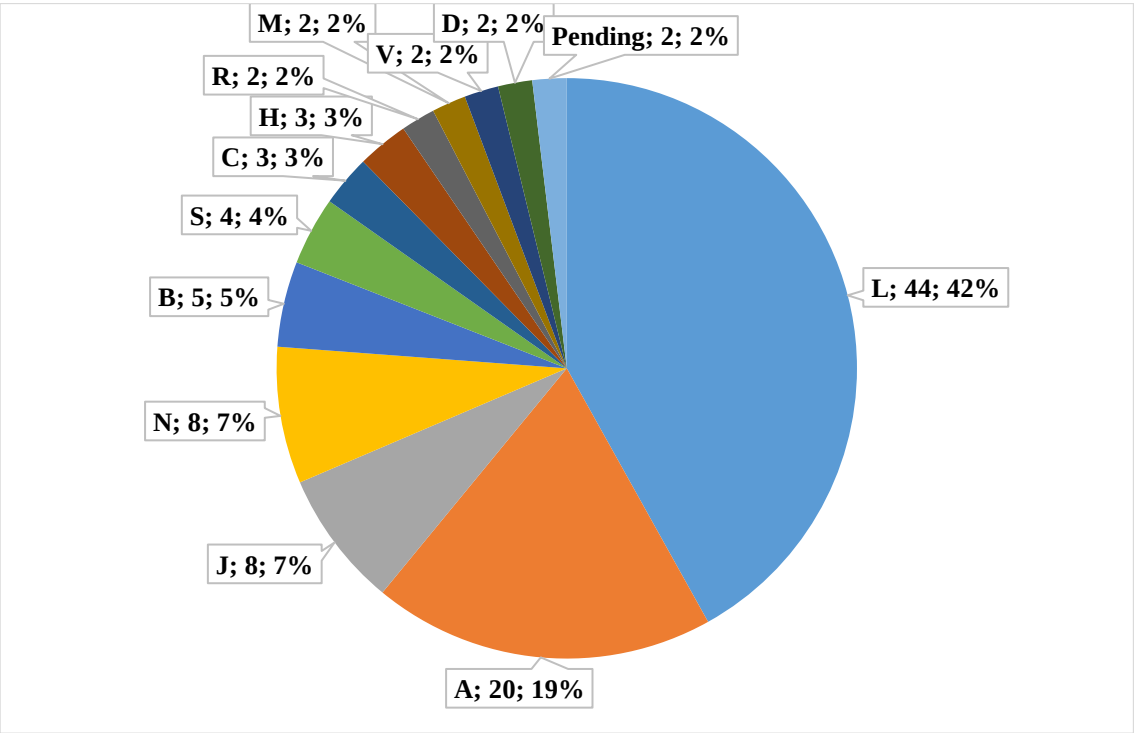


**Figure 8:** Distribution of Orphan Drugs according to ATC Codes

*Pending: Product in the designation process of ATC code.

Figure 8 shows the distribution of all drugs on the list of orphan drugs according to ATC Codes. When analyzed ATC codes of orphan drugs, it has been observed that L - Antineoplastic and Immunomodulating Agents is the most common ATC group. This group is mainly related to oncological or immune system diseases. Following code L, group A- Alimentary Tract and Metabolism enters the list as the second most common group. This group is mainly related to gastrointestinal and metabolic diseases.

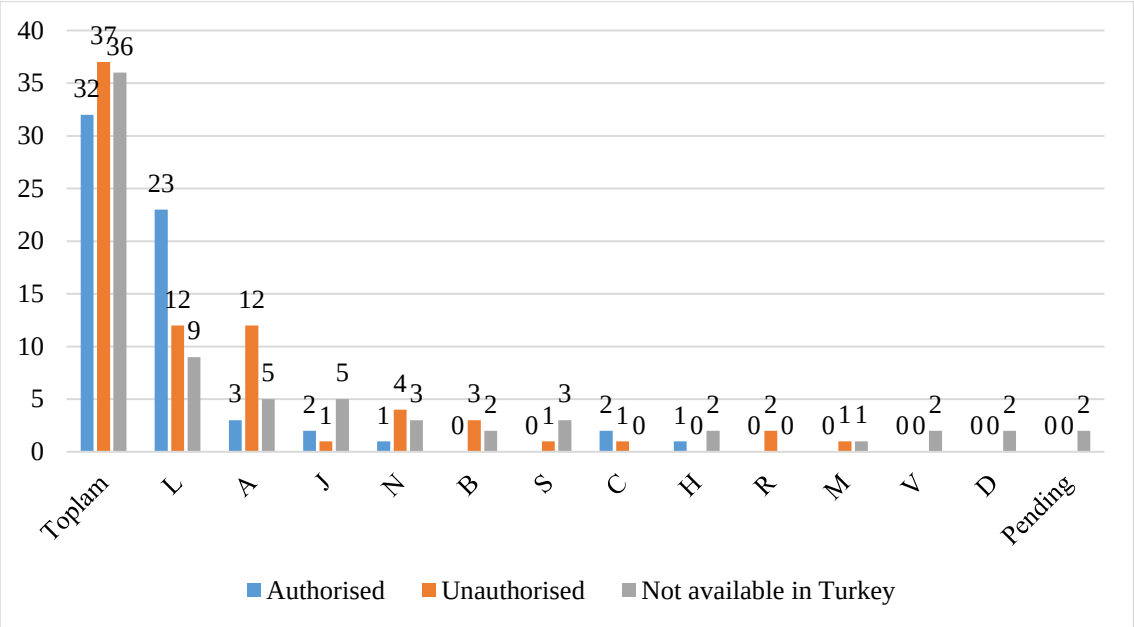


**Figure 9:** Authorization and access status of orphan drugs according to ATC codes

*Pending: Product in the designation process of ATC code.

When analyzed Figure 9, it is seen that 23 out 32 authorized products (~72%) belong to group L. There are no products in groups B, S, R, M, V, D or in the designation process of ATC codes. Out of 37 authorized products, 12 products belong to group L and 12 products are in group A. Out of 36 medical products which are not accessible in Turkey, 9 products are in group L. The reason why all kinds of features are indicated for group L more than any other group, is that 42% of the medical products in the list comprise of group L.

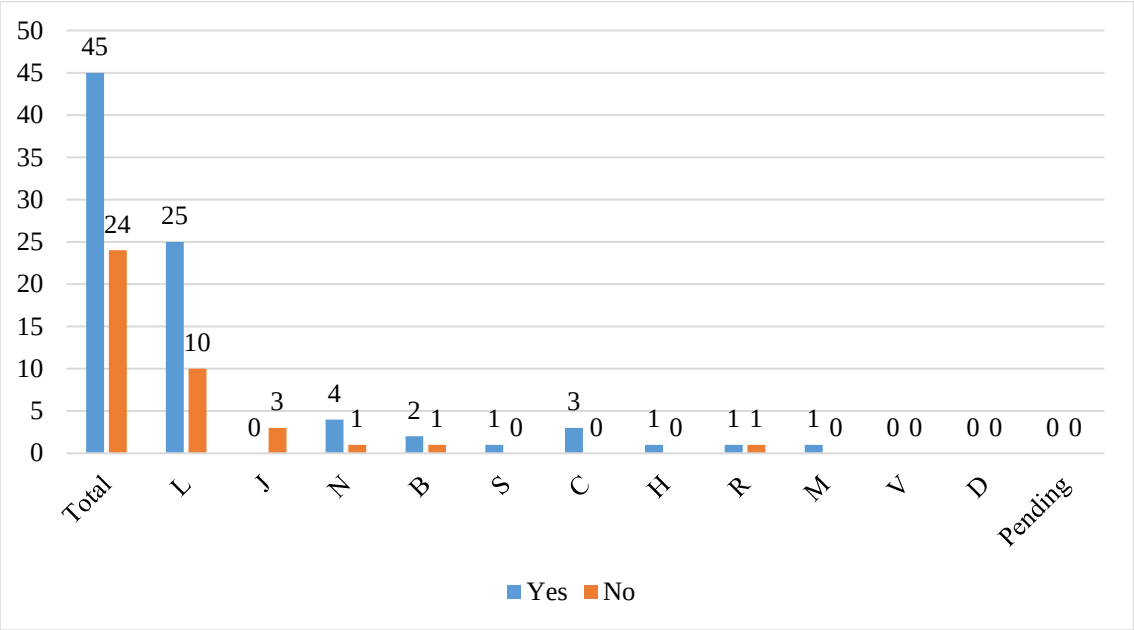


**Figure 10:** Reimbursement status of orphan drugs accessible in Turkey according to ATC codes

*Pending: Product in the designation process of ATC code.

In Figure 10, it is seen that out of 69 orphan drugs which are accessible in Turkey, 45 drugs (65%) are under reimbursement while 24 drugs (35%) are not under reimbursement. When analyzed on the basis of ATC codes, most drugs under reimbursement are the ones coded L. This is primarily because 42% of the products listed are coded with L. None of the orphan drugs products with ATC Codes of J, V and D and those in the designation process of ATC codes are not under reimbursement.

**Table 3:** Annual Total Number of Boxes- Prices and Budgets of Orphan Drugs (€)

| | | |
|---|---|---|
| **2016** | Price (€) | 87,061.94 |
| | Number of Boxes | 192,278 |
| | Budget (€) | 274,735,980.58 |
| **2017** | Price (€) | 83,927.08 |
| | Number of Boxes | 217,917 |
| | Budget (€) | 285,062,258.89 |
| **2018** | Price (€) | 202,245.72 |
| | Number of Boxes | 268,755 |
| | Budget (€) | 188,795,010.92 |
| **Overall** | Price (€) | 356,075.79 |
| | Number of Boxes | 678,950 |
| | Budget (€) | 474,119,450.81 |

Table 3 shows the total number of boxes, prices and budgets of orphan drugs between 2016 and 2018. Although the number of boxes of purchased orphan drugs has increased each year, no continuous increase or decrease is observed in the prices or budgets.

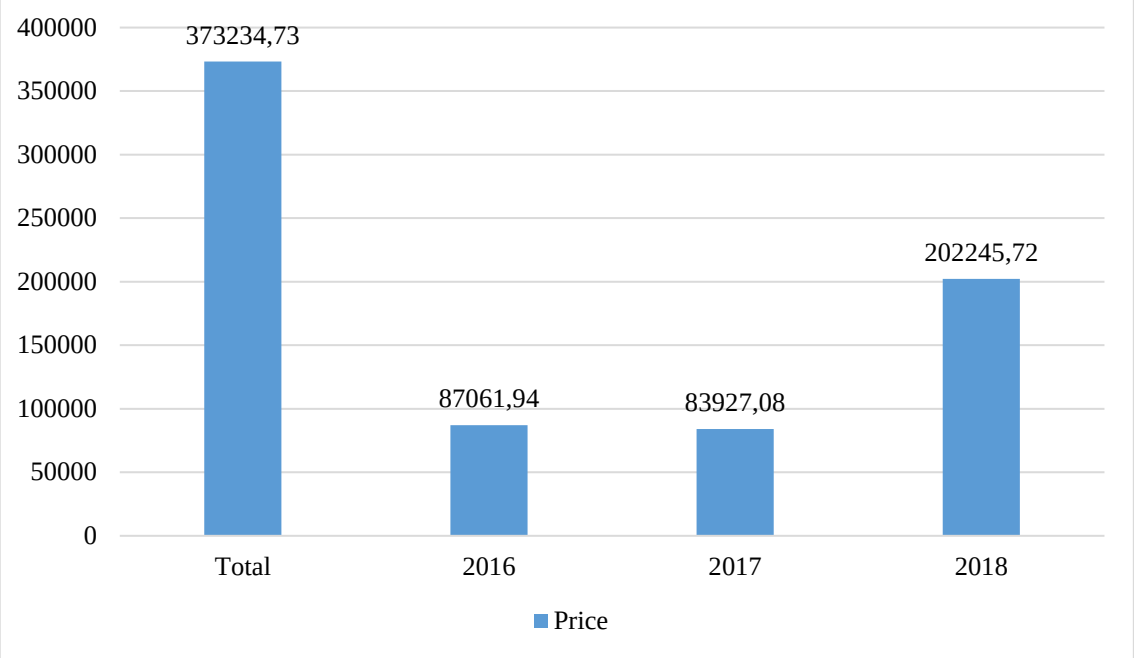


**Figure 11:** Annual Distribution of Orphan Drugs (€)

Figure 11 shows the total unit (box) prices of orphan drugs. The reason behind the increase in 2018 is not the increase in drug prices but the fact that more drugs have got into the market.

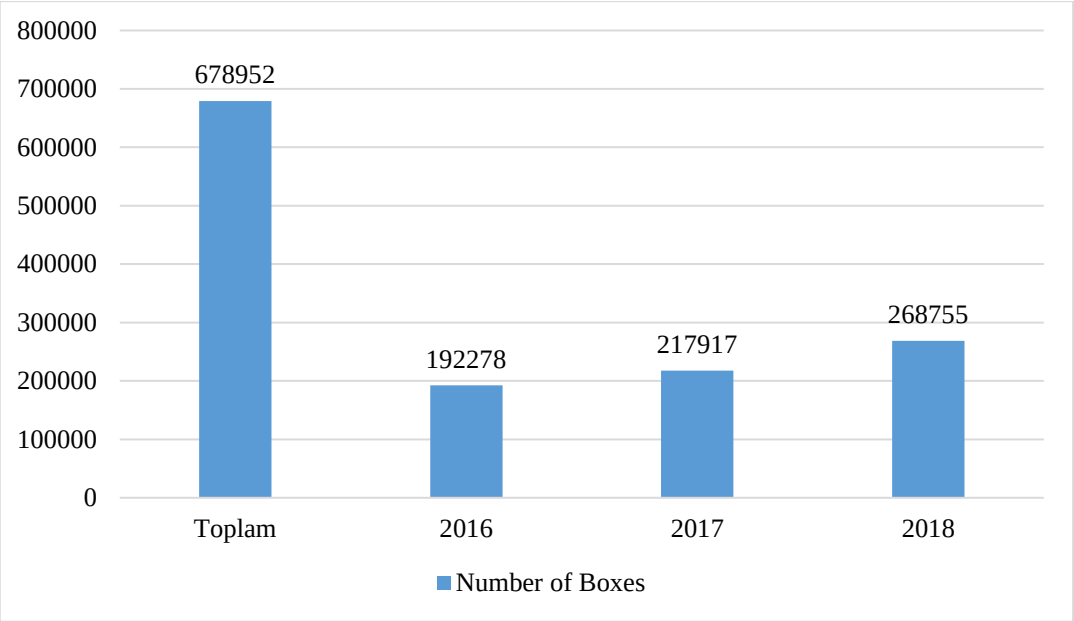


**Figure 12:** Annual Distribution of Number of Boxes for Orphan Drugs

As it is shown in Figure 12, the number of orphan drugs getting into the Turkish market on the basis of boxes is increasing each year.

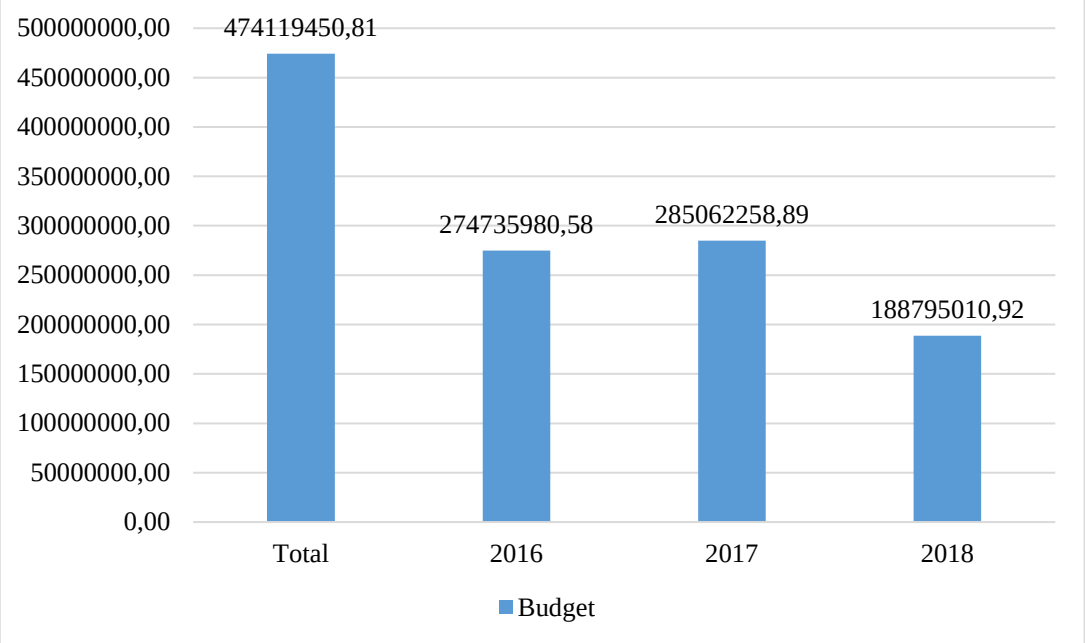


**Figure 13:** Annual Budget Distribution of Orphan Drugs (€)

In Figure 13, the budget of 2018 is expected to be higher based on previous data. However, one of the reasons why it is lower than expected is that there are more relatively cheaper products on the basis of boxes.

**Table 4:** Annual Number of Boxes- Prices and Budgets of Orphan Drugs according to ATC Codes (€)

| | **2016** | | | **2017** | | | **2018** | | |
|---|---|---|---|---|---|---|---|---|---|
| **ATC Code** | **Price (€)** | **Boxes** | **Budget (€)** | **Price (€)** | **Boxes** | **Budget (€)** | **Price (€)** | **Boxes** | **Budget (€)** |
| L | 58,193.09 | 103,241 | 192,357,845.75 | 55,947.76 | 124,450 | 201,152,179.48 | 57,996.86 | 143,829 | 86,158,642.87 |
| A | 6,778.68 | 36,627 | 38,361,206.31 | 7,363.97 | 40,020 | 41,033,956.86 | 35,198.303 | 71,732 | 65,568,996.77 |
| J | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| N | 4,490.36 | 27,346 | 1,455,771.33 | 4,487.29 | 24,475 | 1,318,115.45 | 94,546.50 | 16,979 | 3,342,581.06 |
| B | 3,252.13 | 11,533 | 30,778,335.97 | 3,252.13 | 10,742 | 27,777,772.59 | 3,152.13 | 6,950 | 16,583,995.77 |
| S | 195.00 | 4,965 | 968,175.00 | 655.00 | 2,600 | 1,703,000.00 | 655.00 | 4,551 | 2,980,905.00 |
| C | 4,633.11 | 6,402 | 4,681,376.05 | 4,186.30 | 14,184 | 9,154,245.38 | 3,627.04 | 24,034 | 13,494,312.59 |
| H | 4,756.53 | 384 | 634,148.89 | 3,271.60 | 580 | 6,355,90.01 | 2,642.89 | 662 | 585,890.86 |
| R | 336.04 | 582 | 195,575.28 | 336.04 | 378 | 127,023.12 | 0 | 0 | 0 |
| M | 4,427.00 | 1,198 | 5,303,546.00 | 4,427.00 | 488 | 2,160,376.00 | 4,427.00 | 18 | 79,686.00 |
| V | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TOTAL** | **87,061.94** | **192,278** | **274,735,980.58** | **83,927.08** | **217,917** | **285,062,258.89** | **202,245.72** | **268,755** | **188,795,010.92** |

Table 4 shows the total number of boxes of orphan drugs yearly and according to ATC codes. For all years and categories, the largest portion comprises of products coded L according to ATC classification system.

## 5. DISCUSSION and CONCLUSION

Updating the national policy is of importance for rare diseases and orphan drugs. For researchers, incentives to carry out domestic clinical researches for diagnosis and treatment of rare diseases should constitute the substantial part of this policy. Furthermore, legal texts should be created in a powerful way so as to ensure that patients access therapies faster. Late diagnosis, late arrivals of patients to the right centers, insufficient number of drugs used in treatment of patients, problems faced with procurement of drugs, high costs of drugs put both patients and scientists researching these diseases in a difficult situation. Several problems are encountered due to lack of knowledge and experience in rare diseases, insufficient number of specialist physicians in the field and challenges in treatment and follow-up of patients. All these reasons require an effective unit on Rare Diseases and Orphan Drugs within the Ministry of Health to work actively in order to conduct reviews and inspections and draw up relevant legislation. Creating awareness of rare diseases and orphan drugs will also contribute to the solution in this context. To create aforesaid awareness and reduce the social burden concerning the solution of problems that patients encounter socially or due to absence of policies, cooperation and support of all the responsible stakeholders such as associations of patients and patient relatives, doctors, specialized associations, political agents and sector representatives will make significant contribution (4).

Policies developed by the governments for R&D and marketing processes of orphan drugs which need to be produced for the treatment of rare diseases are significant, considering each country's population affected by rare diseases. In Turkey, as it is indicated in the Regulation on Clinical Research, applications must be made directly to the Ministry of Health in order to conduct research on diseases of which the treatment is not yet known adequately and require clinical research and on orphan drugs which are to be produced tailor-made for these diseases. Pharmaceutical industry have little interest in orphan medical products because the number of patients is limited under normal market conditions. Therefore, the EU offer pharmaceutical companies incentives for R&D (24).

However incentives given to companies to develop orphan drugs are inefficient for both society, patients and industry due to limited by financial constraints. In particular, if incentives are to be given to develop orphan drug, they should go beyond the market exclusivity of patient access and reimbursement. In some cases, standard HTA procedures are insufficient to fully demonstrate the social value of health technologies

such as medicines, medical devices, surgical procedures and health care systems. Therefore, if the issue is the development of orphan drugs or the treatment and financing of rare diseases, rigorous approach is required into the methods of assessing the societal value of these health technologies.

### 5.1. National Strategy Recommendations to Accelerate Research and Product Development and Establish Awareness for Rare Diseases

As mentioned earlier, implementation of certain policies by the public is required for the developing orphan drugs. Recommendations for these policies are provided below (34):

- Active involvement and collaboration of various public and private parties such as commercial companies, governmental agencies, researchers, academic institutions, and advocacy groups
- Applying of improvements in technology and science on time which raise developments on researches and products faster, easier, and cheaper
- Creating new strategies and ensuring high involvement of people who are suffering from rare diseases in researches and using scarce funding, expertise, data, biological specimens efficiently by sharing research resources
- In order to overcome the difficulties of carrying out a research on small populations such as rare diseases; using appropriately specially developed design and analytic methods and developing new methods
- Rational usage of public resources to develop products if the innovation of private sector is supported by reasonable rewards and if there is a faster and more cost effective way to supply unmet needs
- Adequate organizations and resources on research and development of drugs on rare diseases such as experts working public agencies that finance biomedical researches and responsible regulatory of drugs and medical devices
- Mechanisms for determining priorities for research, developing product for rare diseases and establishing collaboration and also mechanisms for determining company objectives and assessing progress towards objectives

### 5.2. Orphan Drug Status in Turkey

36 out of 105 orphan drugs given in the list of EMA are not accessible in Turkey. Out the remaining 69 orphan drugs, 45 products are under reimbursement in Turkey. 16 of those 45 products are under reimbursement through Alternative Reimbursement.

When analyzed the ATC codes of the orphan drug list, L - Antineoplastic and Immunomodulating Agents is observed to be the most common group in the list. This group covers oncological or immune system diseases. The second most common code in the orphan drug list is A - Alimentary Tract and Metabolism group. This group covers gastrointestinal and metabolic diseases.

Authorization and accessibility statuses of orphan drugs in Turkey have been analyzed on the basis of ATC codes. Out of 32 authorized products in the list, 23 are coded L; 3 of them are A; 2 of them are C; 2 of them are J; 1 of them is N and 1 of them belongs to group H. Products coded L comprise about 72% of the authorized products.

When analyzed the reimbursement status of orphan drugs on the basis of ATC codes, with 25 products, most drugs under reimbursement are the ones coded L. As for the groups which are not under reimbursement, 3 of the products coded J are accessible in Turkey. Yet, none of them have been included in the scope of reimbursement. Products with ATC codes of V and D, and those which are in the designation process of ATC codes are not accessible in Turkey.

The prices of the products listed on a unit box basis total €373,234.73 for 3 years. The price in 2016 is €87,061.94, and €83,927.08 in 2017 and €202,245.72 in 2018. The deviation in 2018 was caused by the drugs which were included in the orphan drug list in that year. Thus the most expensive product in the list of orphan drugs is Spinraza with €90,0000 unit price. This product started to be sold in Turkish market in 2018. Although it is rather difficult for such high priced products to be under reimbursement, having seen through the perspective of social conscience, Spinraza has been included in scope of reimbursement.

When analyzed the distribution of the products listed on a box basis, Turkey has purchased a total of 678,950 boxes of drugs within 3 years. Of those drugs, 192,278 were purchased in 2016; 217,917 of them in 2017; and 268,755 of them were purchased in 2018. It can be said that Turkey purchased more drugs on a box basis each year.

When analyzed the impact of the products in the list on the budget, the total budget for 3 years is €748,593,250.39. The orphan drug budget for 2016 is €274,735,980.58, the

budget for 2017 is €285,062,258.89 and the budget for 2018 is €188,795,010.92. The budget for 2018 was expected to be more, because the number of boxes purchased and the total unit price of the products are higher compared to other years. Besides, Spinraza, which is worth €90,000.00, was first purchased in 2018.

Despite all the biggest role of decline in 2018 budget could belong to products in group L, which have th higest budget and weight among all orphan drug groups of the ATC code. This deviation could be due to the fact that the payer change their payment channels in ways other than the classic ways. For this group of medicines reimbursement could be provided via the normal procedure, by increasing the number of licensed products. In this way burden of budget could be decreased by calculating the reimbursed prices with fixed currency rate, instead of current currency rates. A striking example of this would be the drug called Soliris.

Another reason behind the declining of the budget could be restricting or removing other product groups from the list in order to establish ability to pay for products which are expensive and important for the perspective of social conscience such as Spinraza.

The increase in the number of boxes can be explained by the purchase of more drugs with cheaper unit price.

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# ANNEX I

# CURRICULUM VITAE

**Personal Informations**

| | | | |
|---|---|---|---|
| **Name** | Sibel | **Surname** | Atalay |
| **Place of Birth** | Ankara | **Date of Birth** | 06.08.1980 |
| **Nationality** | Turkey | **TC ID Number** | 42313778016 |
| **E-mail** | s.atalay@genilac.com | **Phone Number** | +905558379545 |

**Education**

| Degree | Department | The name of the Institution Graduated From | Graduation year |
|---|---|---|---|
| **Master** | Yeditepe University | Institute Of Health Sciences | 2020 |
| **University** | Hacettepe University | Faculty of Pharmacy | 2002 |
| **High School** | Kurtuluş High School | Science | 1998 |

| Languages | Grades* |
|---|---|
| English | Good (2009 ÜDS: 82,5) |
| | |

* If there is more than one exam (KPDS, ÜDS, TOEFL, EELTS etc.), all the results should be written.

**Work Experience (Sort from present to past)**

| Position | Institute | Duration (Year-Year) |
|---|---|---|
| Gen İlaç ve Sağlık Ürünleri San.ve Tic. A.Ş. | Regulatory Affairs Manager | Jan.2016-Present |
| Astra Zeneca | RA Operations Executive | Oct.2015-Jan.2016 |
| Covidien Sağlık A.Ş. | Regulatory Affairs Manager | Agu.2010-May.2014 |
| Sanofi | Official Affairs Specialist | Oct.2005-Nov.2009 |
| Servier | Medical Delegate | Agu.2002-Oct.2005 |
| Novartis | Quality Control Intern | Haz.2001-Sept.2001 |

**Computer Skills**

| Program | Level* |
|---|---|
| Word, Excel, Power point | Good |
| | |

* Excellent, good, average or basic