Analysis of Patient Access to Orphan Drugs in Turkey

GÜVENÇ KOÇKAYA (guvenc@kockaya.net)
ECONiX Research Analysis and Consultancy Plc. https://orcid.org/0000-0003-3996-7975
Sibel Atalay
Yeditepe University: Yeditepe Universitesi
Gulpembe Oguzhan
Ondokuz Mayis University: Ondokuz Mayis Universitesi
Mustafa Kurnaz
Econix Research Analysis and Consultancy Plc.
Selin Okcun
Econix Research Analysis and Consultancy Plc.
Cigdem Sar Gedik
Health Economics and Policy Association
Mete Saylan
Health Economics and Policy Association
Nazlı Sencan
Acıbadem Üniversitesi: Acibadem Universitesi

Research

Keywords: rare disease drug, orphan drug, orphan drug market

Posted Date: October 21st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-93956/v1

Version of Record: A version of this preprint was published on February 6th, 2021. See the published version at https://doi.org/10.1186/s13023-021-01718-3.

Abstract

Background: Rare diseases are life-threatening, serious, and chronic genetic conditions that require complex care and have a low prevalence. An estimated one in 15 people worldwide are affected by rare diseases. This study aims to analyze the accessibility, reimbursement status, licensed status, and Anatomical Therapeutic Chemical (ATC) codes of drugs that the European Medicines Agency (EMA) in Turkey considers to be “orphan” pharmaceuticals.

Methods: The drugs included in this analysis were obtained from the list of orphan drugs published by the EMA. Orphan drugs’ accessibility and licensing status in Turkey were obtained from the *Health Implementation Communiqué* published by the Social Security Institution (SGK) and the *List of Abroad Active Substance* and *List of Licensed Products* published by the Turkey Pharmaceuticals and Medical Devices Agency (TİTCK). Descriptive analysis was applied to determine the accessibility status of orphan drugs identified by the EMA in Turkey.

Results: Based on the EMA, 105 pharmaceuticals were approved with “orphan drug” status by January 2020. Of the 105 rare drugs on the EMA list, 34 were inaccessible in Turkey. Of the 71 available drugs, 23 (32%) were licensed and 48 (68%) were unlicensed in Turkey. Seventeen licensed products (74%) and 17 unlicensed products (35%) were covered by reimbursement. When orphan drugs’ ATC codes were examined, the most common ATC group was found to be “L –Antineoplastic and Immunomodulatory” agents.

Conclusion: An orphan drug incentive policy is very important to ensure early access to the drugs used to treat rare diseases. It is obvious that such a policy must prepare for the regulation of orphan drugs in Turkey.

Introduction

Health problems affect people physiologically, psychologically, socially, and economically, and they may prevent people from continuing their lives functionally.[1] Rare diseases may seen rare in society, however they are one of major health problems as life-threatening, serious, genetic,[2] chronic,[3] complex,[4] and demanding[5] conditions. Rare diseases are usually genetic in origin—such as cancer, autoimmune diseases, and degenerative and proliferative diseases—except for rare diseases originating from infection and infestation.[2]

Although the definition of “rare disease” varies, diseases that affect fewer than 200,000 people in the United States (US), 50,000 people in Japan, and 2,000 people in Australia are considered “rare”.[3,6] The World Health Organization (WHO), according to a report published in 2013, considers a disease to be “rare” if it affects fewer than five people per 10,000.[3]

In general, rare diseases range in prevalence from one to eight people per 10,000.[6] An estimated 25 million people in the US, 30 million people in Europe, and 400 million people worldwide are affected by

rare diseases.[3] Although each rare disease affects a small number of people, 6–10% of the overall population is affected[3] by a rare disease.[3]

World epidemiological data are constantly changing. Although a new rare disease is discovered almost every week, its status may change from being considered a rare disease[2] to being described as a common disease.[2]

On the one hand, because rare diseases occur in unusual forms and often entail comorbidities, they are difficult to diagnose. On the other hand, no diagnostic methods or diagnostic possibilities are available for many rare diseases. Also, the number of doctors who can diagnose and treat rare diseases is very limited. Therefore, appropriate treatment is difficult to obtain, and patients sometimes spend many years facing treatment uncertainty.[4,7]

Estimates suggest a total of 8,000–10,000 rare diseases.[8] Drugs have been approved to treat approximately 300 of these diseases. In other words, no appropriate treatment is available for approximately 95% of rare diseases.[9]

Orphan Drugs

An “orphan drug” is a drug especially developed to treat a rare medical condition. The high costs of drug development and pharmaceutical companies’ reluctance to develop drugs for very small patient populations make the public sector’s participation in the orphan drug market critical.[10]

The *Orphan Drug Act* was adopted in 1983 in the US to facilitate the research, development, and commercialization of drugs to treat rare diseases that are largely ignored.[11] Orphan drug legislation and policy have succeeded in promoting the progression of treatments for rare diseases. Since these policies’ implementation, more orphan drugs have been licensed in the US.[12,13]

Market access to orphan drugs faces several challenges, including delays in the process from European Medicines Agency (EMA) approval to reimbursement. In some European countries, reimbursement takes longer for orphan drugs than other drugs. The main reason for this difference is that European countries, unlike the US, include health technology assessment (HTA) processes. A limited number of HTAs on orphan drugs[14] are available, and negative results are generally obtained when standard HTA procedures are applied to orphan drugs.[15,16]

In a study that covered August 2000 to December 2004, only 18 of 255 orphan drugs (7.1%) in Europe were approved. Meanwhile, 153 out of 193 drugs (79.3%) for which applications had been submitted to the EMA during the same periods received license approval.[17]

The Orphan Drug Market

Marketing authorization for a drug does not mean that the drug is available in all countries within the European Union.[18] Marketing authorities determine commercialization status in each country. The necessary procedures are then applied to determine a drug's reimbursement conditions and price.[19] In most countries, access to orphan drugs is only possible if it is included on the country's reimbursement list. Figure 1 compares the number of orphan drugs on the market that are unavailable in European countries.[14]

Rare Diseases and Orphan Drugs in Turkey

Inevitably, the problems with rare diseases throughout the world are also experienced in Turkey. Rare diseases occur frequently in Turkey due to disease burden, consanguineous marriages, and different ethnic structures.[18] In Turkey, the Ministry of Health on the Pricing of Medicinal Products for Human Communiqué (2007) defined "orphan drugs" as drugs for the treatment of a disease affecting a population of more than 100,000.[20] It could be said that the definition of the prevalence of rare diseases in Turkey is very low compared to the European Union and United States.[21]

The number of rare disease specialists, insufficient knowledge or experience, and expensive treatment processes are leading problems. The preparation of regulation on rare diseases and orphan drugs is expected to facilitate more concrete steps in diagnosis, treatment, and disease prevention for both researchers or physicians and patients.[22]

To determine specific orphan drug legislation in Turkey, since the beginning of 2010, the Turkey Pharmaceuticals and Medical Devices Agency (TİTCK)—formerly known as the Pharmaceutical General Directorate—has conducted detailed studies.[23] The main purpose of the agency's *Draft Guidance Document* (still not public) was to encourage research on treatments for rare diseases, develop appropriate treatment alternatives, provide incentives for placing these treatments on the market, and determine orphan drug identification criteria as well as authorization requirements.[21]

In Turkey, the TİTCK is following orphan drug operations in three ways. A drug:

1. can be licensed and available for purchase on the market;
2. can be currently not licensed in Turkey but available by prescription if approved in the US or the EU, efficacy and safety grounds are provided, and a clinical trial protocol is available;
3. can be available for patients approved under the compassionate use program or with early access to a humanitarian medication to be clinically administered.[11,21]

In Turkey, in accordance with the *Regulation on Medicinal Products for Human Use Permit*, the Ministry of Health completes a preliminary examination within 210 days of the date an application is submitted. If the drug complies with legal regulations, its application is finalized. The same regulation also states that it can issue licenses if it cannot provide absolute evidence for sufficient effectiveness and safety in rarely indicated indications for an orphan drug application.[24]

A protocol has been signed between the Turkish Ministry of Health and the Turkish Pharmacists' Association (TEB) to supply drugs from abroad that are otherwise unavailable in Turkey, whether licensed or unlicensed. According to this protocol, the provision for the supply of units from abroad was created by the TEB, which serves as an economic operator. The association's Ankara-based units have branches in Istanbul, Izmir, and Adana. Drugs for rare diseases claimed to have been purchased abroad through this unit are sent to patients and their relatives.[25] Like the TEB, the Social Security Pharmaceutical Department of the Social Security Center, Ibn Sina, Pharmaceutical Warehouse within the Social Security Institution (SGK) supplies drugs from abroad[26].

This study aimed to analyze the accessibility, reimbursement status, licensed status, and Anatomical Therapeutic Chemical (ATC) codes of drugs considered "orphan" by the EMA in Turkey. In addition, orphan drug data taken on a box basis and the budget allocated to these drugs were calculated according to the years. Accordingly, the study's findings evaluated orphan drug policy and drugs' access statuses.

Method

Data Set

A general literature review was performed using Google Scholar, Google Books, the National Thesis Center, ProQuest, and Orphanet databases with the "rare disease" and "orphan drugs" keywords. In addition to the literature review, in order to perform the study's analysis, a list of essential drugs was obtained from the official websites of the EMA, TİTCK, SGK, and the Association of Research-Based Pharmaceutical Companies. Turkey does not have an orphan drug list published by the Ministry of Health. For this reason, the drugs listed in the "List of Medicinal Products for Rare Diseases in Europe" published at www.orpha.net and www.orphadata.org were accepted as orphan drugs to be included in this analysis.

The official TİTCK and SGK websites were accessed for orphan drugs' public cost data. Orphan drugs' access and licensing statuses in Turkey were obtained from the *Health Implementation Communiqué* published by the SGK and the *List of Abroad Active Substance* and *List of Licensed Products* published by the TİTCK. Pharmaceutical costs were based on drugs' sale prices. Costs provided by the SGK in Turkish lira and US dollars were converted into euros, according to the average exchange rate for 2019 published by the Ministry of Treasury and Finance.

Data Analysis

The necessary data were collected on license conditions, access to Turkey, ATC reimbursement restrictions, classification of diseases, and pricing for the quantities and budgets of medicines on the *Orphan Medicines List*.

Table 1 provides ATC codes and their descriptions. The ATC coding system provides the international coding and classification of all molecules that can be licensed and used as drugs. In this analysis, orphan drugs were evaluated on the basis of their ATC codes.

Table 1
ATC Codes and Descriptions

ATC Codes	
L	Antineoplastic and Immunomodulator Agents
J	Systemic Antiinfectives
B	Blood and Blood Making Organs
M	Musculoskeletal System
N	Nervous system
V	Sundry
D	Drugs Used in Dermatology
R	Respiratory system
C	Cardiovascular System
S	Sense organs
H	Systemic Hormone Preparations (Excluding Sex Hormones and Insulin)

The compiled data were transferred to Microsoft Excel. A descriptive analysis was applied to the transferred data.

Results

Access was unavailable in Turkey to 34 of the 105 rare drugs on the EMA list (*List of Medicinal Products for Rare Diseases in Europe*). Therefore, our analysis evaluated 71 rare drugs. Of these 71 drugs, 23 (32%) were licensed in Turkey and 48 (68%) were unlicensed in Turkey (Fig. 2).

Figure 3 shows the distribution of all orphan drugs based on their ATC codes. An examination of orphan drugs based on their ATC codes revealed that the most common ATC group was “L – Antineoplastic and Immunomodulatory” agents. This group usually relates to cancer and the immune system. The second group on the list after Code L was “A – Gastrointestinal Canal and Metabolism.” This group usually relates to gastrointestinal and metabolic diseases. No rare drugs with D or V ATC codes were available in Turkey.

Figure 4 shows that 16 (70%) of 23 licensed products belonged to the L group. None of the B, D, M, N, R, S, or V ATC codes were licensed products. Of the 48 unlicensed products, 12 (25%) belonged to Group L

and 17 (35%) belonged to Group A.

Seventeen licensed products (74%) and 17 unlicensed products (35%) were covered by reimbursement. None of the products from abroad were covered by reimbursement in Turkey. Of the 71 drugs accessible in Turkey, 34 (48%) were covered by reimbursement. The rest were available for patients' out-of-pocket payment.

An analysis on the basis of ATC codes revealed that most of the L-code drugs were included in the reimbursement scope (Fig. 6). The most important reason for this inclusion is that 34% of the products on the list were L-code. None of the orphan drugs with J, V, or D ATC codes were covered by reimbursement.

Table 2
Average Price of Orphan Drugs Based on ATC Code by Years in Turkey

	Price (€)			
ATC Code	**2016**	**2017**	**2018**	**2019**
L	2,327.72	1,804.77	1,526.23	2,330.57
A	3,389.34	2,454.66	5,866.38	4,574.54
J	0	0	0	1,452.57
N	898.07	897.46	13,506.64	31,605.39
B	1,626.07	1,626.07	1,576.07	2,640.00
S	195.00	655.00	655.00	655.00
C	661.87	598.04	518.15	823.24
H	1,585.51	1,090.53	880.96	1,666.07
R	336.04	336.04	0	2,390.39
M	4,427.00	4,427.00	4,427.00	8,115.67
V	0	0	0	0
D	0	0	0	0
Average	**1,802.38**	**1,554.21**	**3,111.47**	**3,907.32**

Table 2 shows the average prices for orphan drugs on an ATC basis in 2016–2019. Drugs with access in Turkey were included in the analysis. It is analysed that average prices increased over the years that investigated. This expected increase is due not only to an increase in drug prices but also to an increase in the number of drugs accessible in Turkey.

Conclusions

Considering the population affected by rare diseases in each country, governments' policies are important in the R&D and marketing processes for orphan drugs necessary for treatment.[27] The pharmaceutical industry has little interest in orphan medicinal products due to the low number of patients in normal market conditions. Therefore, the European Union provides incentives to pharmaceutical companies for research and development.[28,29]

According to 2018 data, the accessible orphan drugs in European countries stand at 91 in Germany, 79 in England, 74 in Austria, 73 in Italy, 68 in France, 66 in Sweden, 61 in Norway, 57 in Denmark, 50 in Portugal, 48 in Spain, 45 in Belgium, and 41 in the Netherlands.[14]

In 2020, of the 105 orphan drugs on the EMA's list, 34 are not accessible in Turkey. Of the 71 remaining items, 34 have reimbursement coverage in Turkey.

The examination of orphan drugs' ATC codes revealed the most common ATC group to be "L – Antineoplastic and Immunomodulating" agents. This group includes treatments for cancer and immune-system diseases. The second-most-common code was "A – Gastrointestinal Canal and Metabolism." This group includes treatments for gastrointestinal and metabolic diseases. An examination of orphan drugs' licensing status based on their ATC codes and access in Turkey showed that, of the 23 licensed products listed, 16 belonged to Group L, two to Group A, two to Group C, two to Group J, and one to Group H. Approximately 70% of licensed products were in Group L.

The examination of orphan drugs' ATC codes based on their reimbursement status in Turkey showed that Group L (17 drugs) was included most often in reimbursement coverage. None of the four products in ATC Group J were available for reimbursement. Products with V and D ATC codes were not accessible in Turkey.

The most expensive product on the list of orphan drugs was Spinraza. Spinraza's unit price was 90,000.00 euros. Pharmaceutical-market sales of this product in Turkey started in 2018, with only 21 boxes initially available. Spinraza is a reimbursement product. Worldwide, after the US and Germany, Turkey has been granted third-place approval to use this drug for 593 patients diagnosed with spinal muscular atrophy (SMA) in the context of reimbursement coverage for drugs

An examination of the drugs' list prices revealed their average price to be 1,802.38 euros in 2016, 1,554.21 euros in 2017, 3,111.47 euros in 2018, and 3,907.32 euros in 2019. The deviation in 2018 was due to Spinraza's unit price of 90,000.00 euros. The increase in average prices in 2019 was due to an increase in the number of drugs.

The analysis based ATC codes seemed to reveal that products in the L Group had the biggest price share and that, from 2018 to 2019, a significant increase occurred in the M, R, and J code groups.

Updating national policy for rare diseases and orphan drugs is critically important. For researchers, the incentives for conducting domestic clinical research on the diagnosis and treatment of rare diseases are an important part of such policy. Moreover, legal texts should be tightly regulated to allow patients faster access to treatment. Late diagnosis, delayed access to appropriate treatment centers, an inadequate number of drugs used in patients' treatment, problems in supplying drugs, and high drug costs present difficulties for both patients and scientists in investigating these diseases. Rare diseases face many problems due to a lack of knowledge and experience, a lack of specialist physicians, and difficulties in patients' treatment and follow-up. For these reasons, an effective unit of the Ministry of Health for rare diseases and orphan drugs should work actively to establish the necessary examinations, inspections, and relevant legislation. The cooperation and support of all responsible stakeholders—such as patients and patients' relatives, physicians, specialists, political actors, and sector representatives—would play a major role in this initiative.

The literature includes no studies that have analyzed reimbursement statuses between 2016 and 2020 in terms of access to orphan drugs, annual use of orphan drugs, and the economic burden of orphan drugs in Turkey. Information on this topic is significantly lacking in the literature. Thus, this study constitutes an important source of information. The authorities and decision maker should take action for raising the awareness of the financial burden facing individuals with rare diseases and their families as well as their difficulties accessing necessary drugs.

Abbreviations

ATC: Anatomical Therapeutic Chemical

EMA: European Medicines Agency

HTA: Health Technology Assessment

SGK: Social Security Institution

SMA: Spinal Muscular atrophy

TEB: Turkish Pharmacists' Association

TITCK: Turkey Pharmaceuticals and Medical Devices Agency

US: United States

WHO: World Health Organization

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding:

No financial support was received for the study.

Authors' contributions:

Data collection, literature review and writing: Selin Ökçün, Mustafa Kurnaz. Data analysis: Guvenc Kockaya, Mete Saylan. Idea, interpretation, revision: Gulpembe Oguzhan, Sibel Atalay, Çiğdem Sar Gedik, Nazlı Sencan. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

References

1. Güneş H. Evaluation of the problems on rare disease and orphan medicines in Turkey with patient perspective. (Master Dissertation). Retrieved from Ulusal Tez Merkezi. (528879):1-5.
2. Azie N, Vincent J. Rare diseases: The bane of modern society and the quest for cures. *Clin Pharmacol Ther*. 2012;92(2):135-139.
3. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, et al. Priority medicines for Europe and the World 2013 Update. WHO Publications. 2013:148-151.

4. Anderson M, Elliott EJ, Zurynski YA. Australian families living with rare diseases: Experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet J Rare Dis*. 2013;8(1):22.
5. Bogart KR, Irvin VL. Health-related quality of life among adults with diverse rare disorders. *Orphanet J Rare Dis*. 2017;12(1):177.
6. Aronson JK. Rare diseases and orphan drugs. *Brit J Clin Pharmaco*. 2006;61(3):243-245.
7. European Commission. Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). Brusells, 2014.
8. Republic of Turkey Ministry of Industry and Technology. Turkey Pharmaceutical Industry Strategy Document and Action Plan 2015-2018. 2015
9. Koyuncu Irmak D. Orphan drugs: Getting arms around rare diseases. *J Comm Pub Health Nurs*. 2017;3(2):1000167.
10. Almalki ZS, Alahmari AK, Guo JJ, Kelton GML. Access to orphan drugs in the Middle East: Challenge and perspective. *Intractable Rare Dis Res*. 2012;1(4):139-143.
11. Koçkaya G, Wertheimer AI, Kılıç P, et al. An overview of the orphan medicines market in Turkey. *Value Health Reg Issues*. 2014;4:47-52.
12. Handfield R, Feldstein J. Insurance companies' perspectives on the orphan drug pipeline. *Am Health Drug Benefits*. 2013;6(9):589-598.
13. Lockhart CM. Value assessment of orphan drugs and treatments for rare diseases. (Master Dissertation). Retrieved from ProQuest. (10138735):1-3.
14. Troein P, Moore T. Orphan drugs in Europe: Availability and supply across the continent. IQVIA 2019.
15. Drummond MF, Wilson DA, Kanavos P, et al. Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess*. 2007;23(1):36–42.
16. Nestler-Parr S, Korchagina D, Toumi M, et al. Challenges in research and health technology assessment of rare disease technologies: Report of the ISPOR rare disease special interest group. *Value Health*. 2018;21;493-500.
17. Joppi R, Bertele V, Garattini S. Orphan drug development is progressing too slowly. *Brit J Clin Pharmaco*. 2006;61(3):355-360.
18. Orphanet Web site: http://www.orpha.net/national/TR-TR/index/yetim-ila%C3%A7lar-hakk%C4%B1nda/ Access Date: 18.05.2019
19. Maresova P, Klimova B, Kuca K. Financial and legislative aspects of drug development of orphan diseases on the European market: A systematic review. *Appl Econ*. 2016;48(27):2562-2570.
20. Official Gazette. Communiqué on the pricing of human drugs. 2007. Number:26651.
21. Koçkaya G, Kılıç P, Yemşen Ö, et al. Orphan drug regulations in Turkey. *Journal of Pharmaceutical Health Service Research*. 2013;4(3):151-153.

22. Köken AH, Büken N. Rare diseases and orphan drugs in the context of the right to health. *Turkiye Klinikleri J Med Ethics Law Hist-Special Topics*. 2018;4(1):91-98.
23. İlaç Bilincini Geliştirme ve Akılcı İlaç Derneği. Nadir hastalıklar ve yetim ilaç sempozyumu: Yetim ilaç yönetmelik çalıştayı. 2014;277-278.
24. Oral M, Özçelikay G. Ethical Overview of Pharmaceutical Industry Policies in Turkey from Various Perspectives. *Turk J Pharm Sci*. 2017;14(3):264-273.
25. Atılgan Karakulak Ö, Doğan D. Distribution and marketing of drugs in Turkey: Overview. Practical Law Country Q&A, 2016;3-4.
26. https://www.teb.org.tr/news/7586/Yurt-D%C4%B1%C5%9F%C4%B1ndan %C4%B0la%C3%A7-Temin-Birimimiz-Taraf%C4%B1ndan-Getirilmekte-Olan-Baz%C4%B1-%C4%B0la%C3%A7lar-Hakk%C4%B1nda-%C3%96nemli-Duyuru Access Date: 29.07.2019
27. Field MJ, Boat TF. Rare diseases and orphan products: Accelerating research and development. National Academies Press. 2011:S3-S4.
28. Nicod E, Annemans L, Bucsics A, et al. HTA program response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. *Health Policy*. 2019;123:140-151.
29. Simoens S, Cassiman D, Dooms M, Picavet E. Orphan drugs for rare diseases: Is it time to revisit their special market access status? *Drugs*. 2012;72(11):1437-1443.
30. Şentürk A, Demir O, Tatar M, et al. Orphan Drug Market Analysis in Turkey. *Value Health*. 2016;19:A581.
31. https://www.medimagazin.com.tr/ozel-saglik//tr-saglik-bakani-basvuru-yapan-199-sma-hastasina-ilac-kullanim-onayi-verildi-9-681-80293.html Access Date: 29.07.2019

Figures

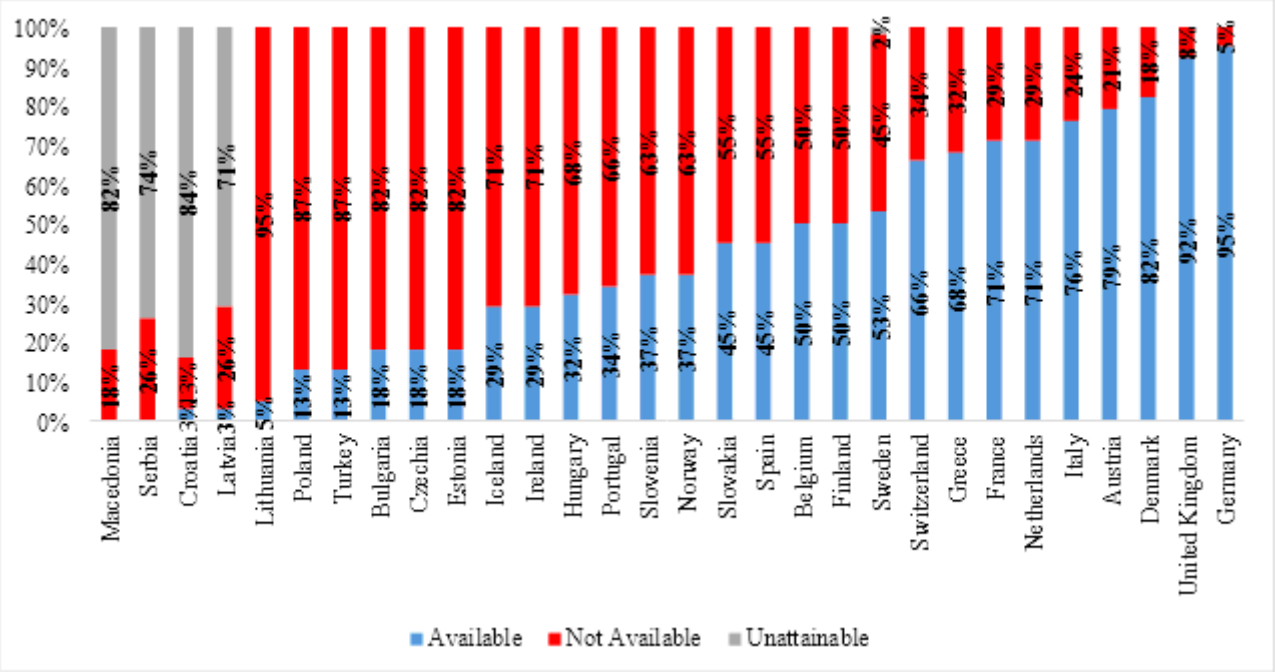

Figure 1

Availability rate measured by the number of drugs available since 201814.

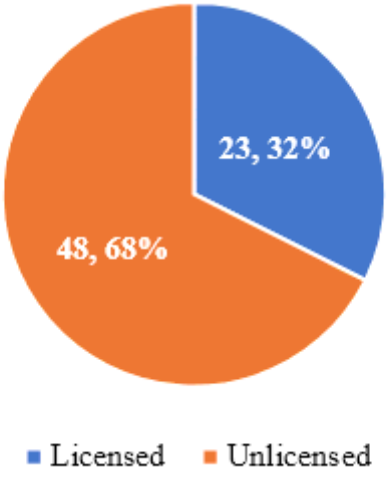

Figure 2

Licensed status of Orphan Drugs in Turkey

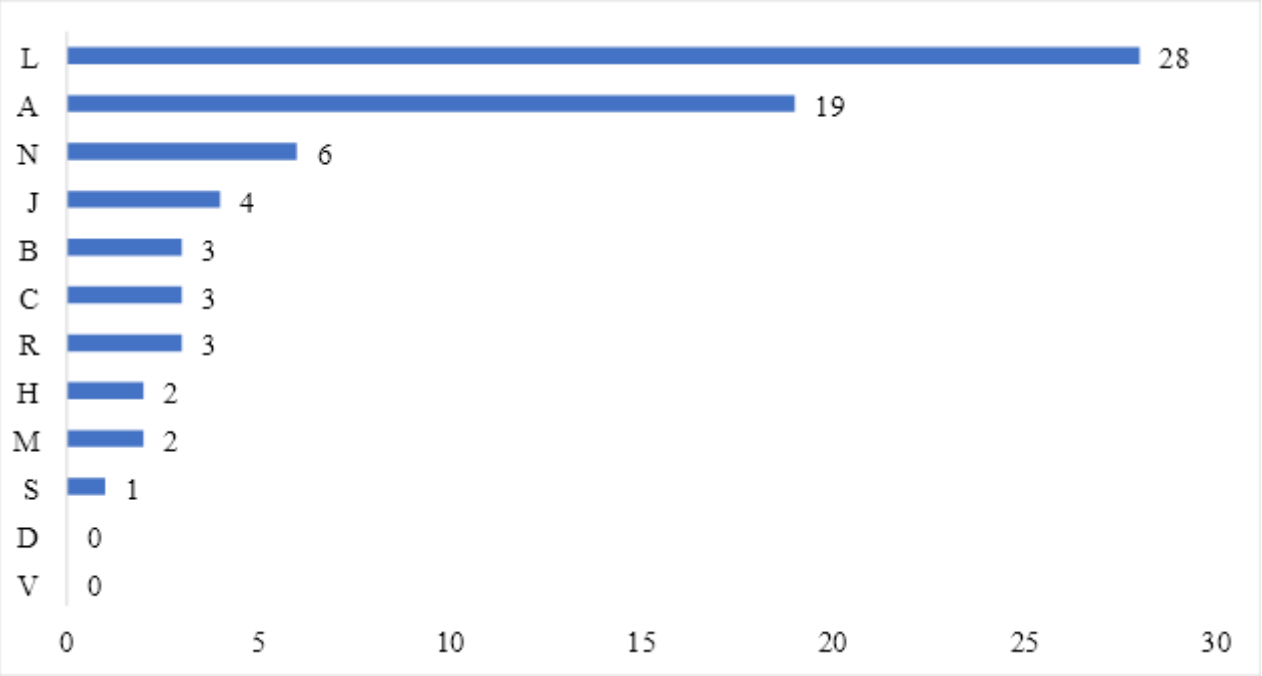

Figure 3

Distribution of All Orphan Drugs in Turkey by ATC Code

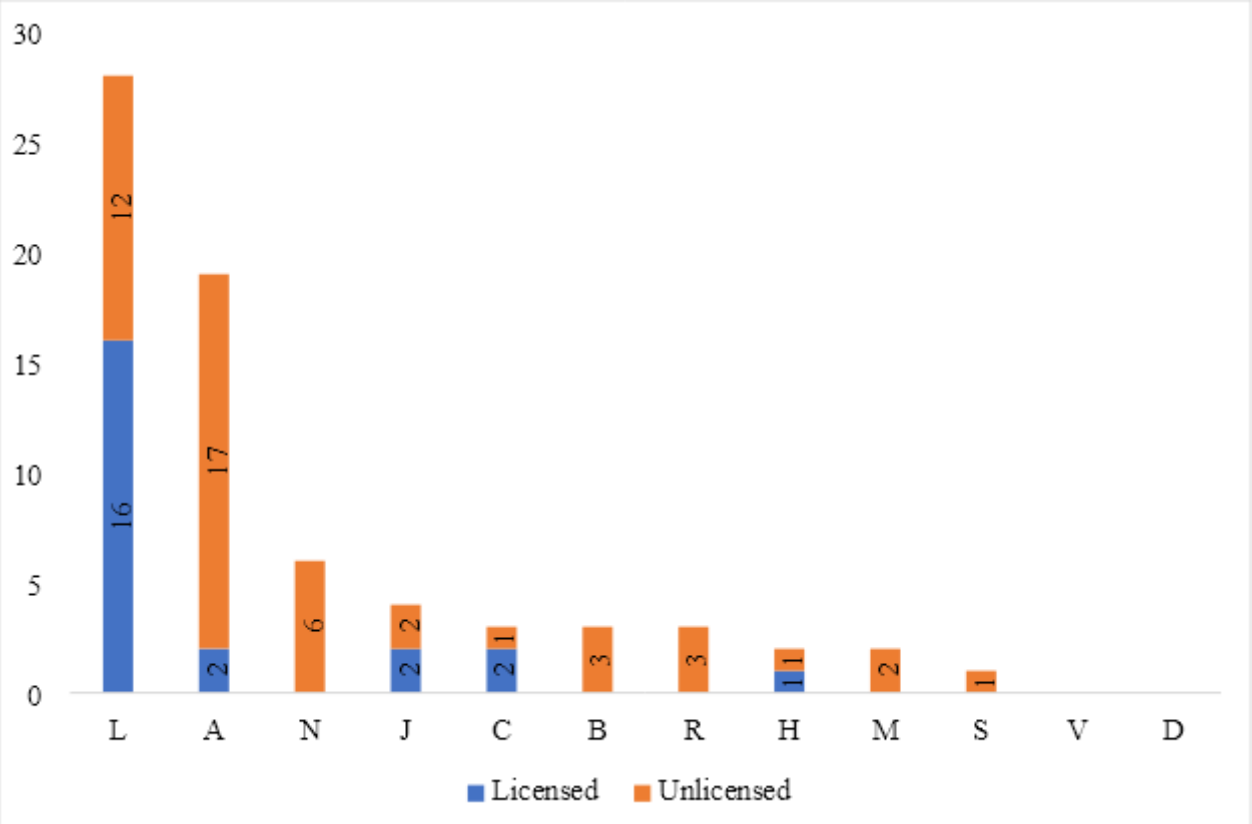

Figure 4

License Status of Orphan Drugs Based on ATC Code

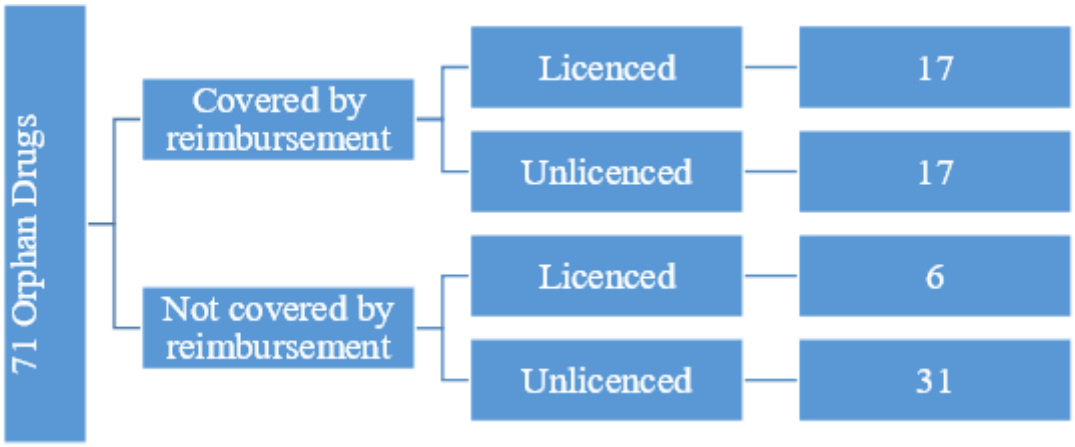

Figure 5

Reimbursement Status of Orphan Drugs Based on Licenced Status

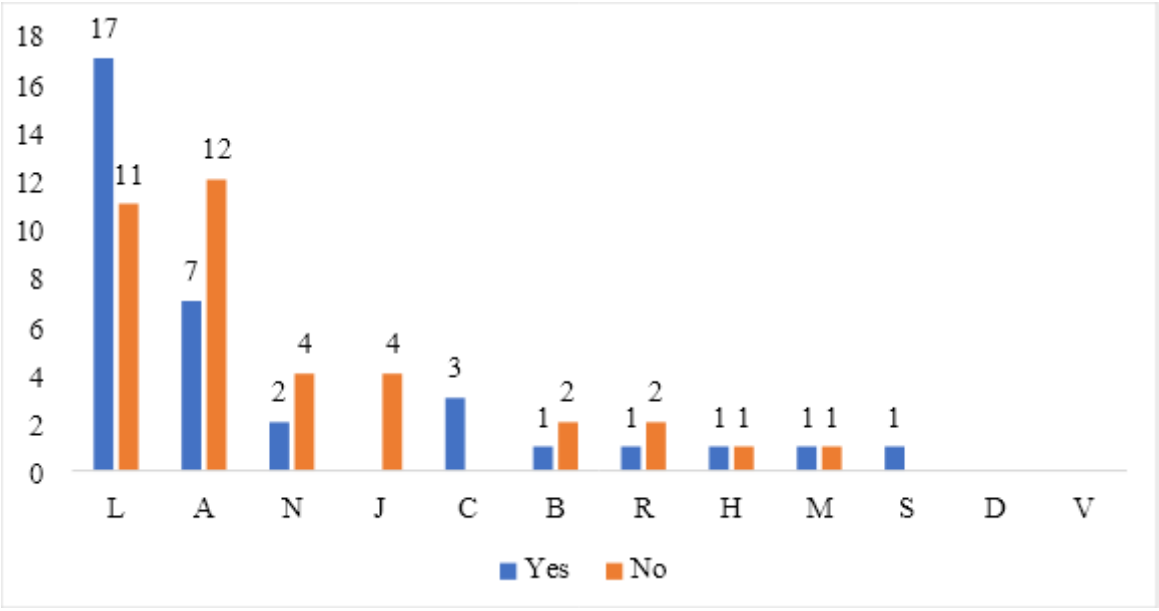

Figure 6

The situation of reimbursement of orphan drugs who have access in Turkey, based on the ATC code.