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ANALYSIS AND EVALUATION OF THE PERFORMANCE OF ALTERNATIVE REIMBURSEMENT AGREEMENTS WITH A PAYER PERSPECTIVE

MASTER THESIS

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APPROVAL

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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.

Okan ATALAY

To my beloved family

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LIST OF SYMBOLS AND ABBREVIATIONS

AIFD	Association of Research-Based Pharmaceutical Companies
ATC	The Anatomical Therapeutic Chemical
EMA	The European Medicines Agency
EU	European Union
EC	European Commission
FDA	Food and Drug Administration
HAC	Hospital Acquired Condition
HTA	Health Technology Assessment
HSPC	Healthcare Services Pricing Commission
IEIS	Pharmaceutical Manufacturers Association of Turkey
R&D	Research & Development
SSI	Social Security Institution
OECD	Social Security Institution
TMMDA (TİTCK)	Turkish Medicines and Medical Devices Agency
TPA	Turkish Pharmacists' Association
TL	Turkish Liras
UK	United Kingdom
US	United States
WHO	World Health Organization

ABSTRACT

Atalay, O. (2020). Analysis and Evaluation of the Performance of Alternative Reimbursement Agreements with a Payer Perspective. Yeditepe University, Institute of Health Science, Department of Pharmacoeconomics and Pharmacoepidemiology, MSc Thesis. İstanbul.

The efforts to improve healthcare services remain to be an important issue in the agenda not only in the developing countries such as Turkey but also in the developed countries. The task for state and politicians is to ensure healthy life and access to drugs for individuals of a community. Thus, each country has developed an individualized reimbursement system. For Reimbursement agreements the most important criteria include clinical effectiveness, safety, quality, cost-effectiveness and ability to pay in reimbursement systems. In our study, it was aimed to evaluate, and report drug-based market access agreements performed in accordance to relevant legislations published in 2016. We used open, published data for our analyses, literature search, relevant legislations, formal publications and reports were screened. Data, descriptive analyses and expert opinion were reported in attempt to provide a basis for further analyses. In Turkey, the first products received alternative reimbursement approval by Healthcare Services Pricing Commission (HSPC) decisions at 18.06.2016 were those used in the treatment of Hepatitis C. 10 products were included to alternative reimbursement coverage in 2016 while 13 in 2017, 24 in 2018 and 10 in 2019. There are 39 pharmaceutical companies having access to Turkish market via alternative payment methods. 57 drugs purchased by alternative reimbursement agreements, 35 were included to 4A List for Drugs reimbursed while 22 were included to 4C Price List for Foreign Medicine. Of drugs included to 4A List for Drugs Reimbursed, 32 are original while 3 are generic drugs. It is seen that vast majority of drugs included to reimbursement coverage are original products. There is no restriction for 24 drugs in 4A List for Drugs Reimbursed and for 18 drugs in 4C Price List for Foreign Medicine. the oncology agents comprise majority of drugs in reimbursement coverage by decision of Alternative Reimbursement Commission when agents are classified based on disease. When assessed according to disorders, it is seen that there are 16 products related to 13 rare diseases. Mean discount rate is found as 33.69% for products in which prices are disclosed. Of 13 products with disclosed price, discount rate from list price is 41% in 8 products. By

establishment of Alternative Reimbursement Commission in accordance with regulations published in 2016, it was aimed to control drug expenses and to deliver treatments with lesser cost through agreements between pharmaceutical companies and reimbursement organization. Sixty percent of drugs added to reimbursement coverage by alternative reimbursement are related with cancer and immune system disorders. When list prices are considered, it is seen that lowest price is 2.51 Euro while highest price is 7991.92 Euro with a mean price of 1572.108 Euro. In general, it should be suggested that agreements based on alternative reimbursement models are advantageous for both public and pharmaceutical companies. Although infrastructure is lacking in our country, there are deficiencies in legislations regarding alternative reimbursement.

Key words: Drugs, reimbursement, drug policies, access to drug.

ÖZET

Atalay, O. (2020). Alternatif Geri Ödeme Anlaşmalarının Performansının Ödeyici Kurum Bakış Açısıyla Analizi ve Değerlendirmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Farmakoekonomi ve Farmakoepidemiyoloji ABD., Master Tezi. İstanbul.

Sağlık hizmetlerini iyileştirme çabaları, yalnızca Türkiye gibi gelişmekte olan ülkelerin değil, aynı zamanda gelişmiş ülkelerin de öncelikli gündem maddesi olmaya devam etmektedir. Devletin ve politikacıların görevi insanların sağlıklı yaşamasını sağlamak ve ilaca erişimi mümkün kılmaktır. Bu sebeple her ülke kendine özgü geri ödeme sistemi geliştirmiştir. . Geri ödemede sırasıyla en önemli kriterler; klinik etkililik, güvenlik, kalite, maliyet etkililik ve ödeyebilme gücüdür. Çalışmamızda Türkiye'de 2016 yılından itibaren geçerli olan mevzuat doğrultusunda yapılan ilaç temelli pazar erişim anlaşmalarının incelenmesi ve rapor edilmesi amaçlanmıştır. Analizin gerçekleştirilebilmesi için yayınlanmış kamuoyuna açık veriler kullanılmıştır. Literatür taramaları, ilgili mevzuat, yönetmelik, duyuru, resmi kurum yayınları ve raporlar incelenmiştir. Veriler, tanımlayıcı analizler ve uzman görüşleri rapor edilmiş olup, ileri analizler için temel olması planlanmıştır. Türkiye'de ilk defa Hepatit C tedavisinde kullanılan ürünler, AGÖK çalışmaları sonucu SHFK kararlarıyla alternatif yöntemlerle 18.06.2016 tarihinden itibaren geri ödeme onayı almıştır. Güncel olarak Alternatif Geri Ödeme sürecinde 57 ilaç bulunmaktadır. Bu ilaçlardan 10 tanesi 2016 yılında 13 tanesi 2017 yılında, 24 tanesi 2018 yılında, 2019 yılında ise 10 tane ilaç Alternatif Geri Ödeme kapsamına alınmıştır. Alternatif geri ödeme yöntemleriyle Türkiye'de pazar erişimini sağlayan 39 ilaç firması bulunmaktadır. AGÖK anlaşmalarıyla alınan 57 ilacın; 35 tanesi 4A Bedeli Ödenecek İlaçlar Listesi'ne, 22 tanesi ise 4C Yurtdışı İlaç Fiyat Listesi'ne eklenmiştir. 4A listesinde bulunan ilaçların ise 32'si orijinal, 3 tanesi jenerik üründür. Alternatif geri ödeme modeliyle geri ödeme kapsamına alınan ilaçların çok büyük kısmının orijinal ürün olduğu görülmektedir. 4A Bedeli Ödenecek İlaçlar Listesindeki ilaçlardan 11 tanesinde geri ödemede kısıtlama olmazken 24 tanesinde kısıtlamalar bulunmaktadır. 4C Yurtdışı İlaç Fiyat Listesindeki ürünlerin ise 18'inde kısıtlama bulunmaktadır. AGÖK kararlarıyla geri ödemeye alınan ilaçların hastalık bazında ayrımı yapıldığında, yoğunluğu onkoloji ilaçlarının oluşturmaktadır. Hastalık bazında incelendiğinde 13 nadir hastalıkla ilgili 16 ürünün bulunduğu görülmektedir. İndirim

oranları açıklanan ürünlerin genel indirim ortalaması %33.69 olarak bulunmuştur. İndirim oranları açık olan 13 ürünün ise 8'inde liste fiyatı üzerinden %41 oranında indirim uygulanmıştır. 2016'da çıkarılan yönetmelik doğrultusunda kurulan Alternatif Geri Ödeme Komisyonu ile ilaç firmaları ve geri ödeyici kurum arasında yapılan anlaşmalarla hem ilaç harcamalarını kontrol altında tutmak hem de ihtiyaç duyulan tedaviyi daha az maliyetle hastalara ulaştırmak amaçlanmıştır. Alternatif geri ödemeyle listeye eklenen ilaçların %60'ı kanser ve bağışıklık sistemi hastalıklarıyla ilgili ilaçlardır. İlaçların liste fiyatlarına bakıldığı zaman; en düşük fiyatın 2,51 Euro, en yüksek fiyatın 7991,92 Euro, genel fiyat ortalamasının ise 1572,108 Euro olduğu görülmektedir. Genele bakıldığında Alternatif Geri Ödeme modelleriyle yapılan anlaşmaların hem kamu hem de firmalar açısından faydalı bir uygulama olduğu söylenilebilir. Ülkemizde konuyla ilgili altyapı bulunmamakla birlikte alternatif geri ödemeyle ilgili mevzuat eksikliği vardır.

Anahtar Kelimeler: İlaç, geri ödeme, sağlık politikaları, ilaç erişimi.

1. INTRODUCTION and PURPOSE

Today, all communities have increased expectations with increase in self-awareness by the rapid evolution and development with advancing technology. The healthcare systems have also been affected by this condition and improvement efforts have been made in healthcare systems in order to fulfill these increasing demand and expectations. All governments have adopted healthcare policies which aim to provide equitably, timely, high quality and effective healthcare services to all individuals. The primary goal of such healthcare policies is to build a sustainable and manageable system [1].

The efforts to improve healthcare services remain to be an important issue in the agenda not only in the developing countries such as Turkey but also in the developed countries. In other words, he need for transformation in healthcare services have been emphasized in the electoral period in all countries, even in United States (US) and United Kingdom (UK). This fact indicates that there is an ongoing effort about novel studies about healthcare delivery across the world. Although there are some variations based on level of development, it is difficult to name a certain country that completely resolved healthcare problems [1].

The cornerstones of healthcare include accessibility to good quality healthcare services, improvement of health outcomes and equitable delivery of healthcare. The increase in population, particularly in elder population; chronic diseases; expanding coverage of health insurance; and alteration in disease profile are markers that will cause evolution in the health [2]. The economical burden of healthcare services is a major concern for all sectors in the community. The individuals, foundations and state deal with challenging decisions about allocation of healthcare sources in face of higher costs of some interventions against perceived benefits. However, the cost is not the only important issue, rather it is important to estimate which intervention produces highest value and to control healthcare costs based on economical considerations [3].

In world, as well as in our country, novel therapeutic agents and treatment modalities are being developed currently. The reasons resulting in increased consumption such as prolonged life expectancy, expanding elder population and increased prevalence of non-contagious diseases together with novel treatment and drug options with high costs produce serious burden [4].

Healthcare expenses can also be problematic in high-income countries as it is the case in the low-income countries. In particularly, this may be a major problem in highly prevalent conditions in particular. Hypothetically, there is an agent that adds an extra-year to life of all individuals and is associated with cost of annual income per capita. Although this agent is classified in high cost-effective category according to threshold defined by World Health Organization (WHO), the delivery of the agent to all appropriate individuals, in other words whole population, would mean to spend whole annual income of a country [5]. This will not be a reasonable approach since one should plan drugs and expenses associated with whole community rather than a single agent or patient group [6].

The task for state and politicians is to ensure healthy life and access to drugs for individuals of a community. Thus, each country has developed an individualized reimbursement system. The aim of reimbursement policies is to protect of health; to ensure access to drugs on an equitable basis; and to control drug expenses in parallel to budget goal of social security organizations. However, social security organizations ensure the delivery of drugs to their members while they take some measures to not overspend for drug expenses by reimbursement policies employed [6]. The most important criteria include clinical effectiveness, safety, quality, cost-effectiveness and ability to pay in reimbursement systems [7].

The availability of pharmaceutical industry is crucial in strategic and economic manner due to its structure relying on high added value and advanced technologies as well as providing healthcare and treatment services with direct impact on human life [8]. However, pharmaceutical industry involves long-term, over-costing research and development (R&D) studies. The pharmaceutical and biotechnology industries are at the top of list when R&D expenses are considered worldwide [9].

Drug licensing, production, pricing, marketing, exporting, promotion, control, rational use, R&D activities, intellectual property rights and burden to state budget and social security organizations by increased drug expenses are among actual problems [1].

In Turkey, drug licensing and pricing processes are managed and audited by Turkish Medicines and Medical Devices Agency (TİTCK) which is governed by Turkish Health Ministry and license application is made to TİTCK by manufacturer of the drug in accordance to "Regulation on Registration of Medicinal Products for Human Use". The reimbursement is made by Social Security Institution (SSI) under supervision of Ministry of Family, Labor and Social Services. The SSI has a social perceptive that aims to ensure

security coverage to whole community with a mission of "to deliver sustainable social security services through reliable, high quality and innovative perceptive by assuring community against changing demands and risk of social security" [10, 11].

Many questions arise regarding reimbursement in health and pharmaceutical industries. In particular, these questions have focused on how payments can be reduced by taking measures in healthcare and pharmaceutical field in recent years. The countries expose both healthcare providers and clients to several problems due to increased complexity of bureaucratic procedures owing the elevations in drug expenses and prices. The responsibility of politicians is to ensure healthy life and access to drug for human and to improve health. Thus, each country has developed a specific reimbursement system. In fact, all reimbursement systems are essentially comparable [6].

In the drug reimbursement system, agents imported comprise a severe burden for budget of SSI, promoting efforts to reduce expenses in this field. The austerity measures also include preferential assessment of imported products in the process of licensing and reimbursement in Turkey [11].

Although rapid evolution in health sector enables more successful and effective struggle with many diseases, excessive R&D expenses of these technologies place payers and patients requiring the novel technology in an awkward position [12]. The Health Technology Assessment (HTA) that refers to systematic, transparent and meticulous evaluation of novel technologies including clinical, economical, organizational, social, legal and ethic implications and comparison with available technology may inform policy makers and clinicians in this process [13]. By increasing importance of HTA, evidence-based reimbursement approach has become more important in the public and private finance of health expenses.

Although the HTA has long been an important phenomenon worldwide, it was brought to agenda in Turkey following Health Transformation Program in 2003. The HTA has become an important matter of fact today and it is operational in certain facilities of SSI and Health Ministry [12].

In Turkey, healthcare expenditure has been increasing constantly since establishment of Health Transformation Program in 2003. The SSI included almost all population in the scope of General Health Insurance. As a result of improved coverage and increased quality of healthcare services, it was attempted to control drug expenses by several regulations; however, no remarkable success could be achieved. It becomes

impossible to maintain sustainability for both payers and pharmaceutical companies, resulting in drawback and delays in the access to novel technologies by patients [14].

In SSI, the balance of income and expenditure was -20,656 million for retirement, health and other services. The SSI has taken some measures over time, including imposing restrictions in drug prices, in order to reduce healthcare expenses. The primary exemplification is not updating Euro exchange rate used to determine drug prices between 2009 and 2015. For the same purpose, restrictions were made in drug expenses between 2010 and 2012 by changes in drug pricing and public allowance rates after implementation of global budget when public drug budget was exceeded [9]. Finally, Alternative Reimbursement Commission, Drug Reimbursement Commission and Medical and Economic Evaluation Commission were implemented as the sub-commissions of Healthcare Services Pricing Commission after publication in official gazette at February, 10, 2016 [15].

The main goal of these commissions is, other than ancestors, principles and regulations, to ensure domestic production or market availability of products exported or those not produced or not available in Turkey which are currently or will be in reimbursement coverage by including product and service groups into reimbursement coverage or modifying regulations in required fields based on economic and medical benefits [15].

The shareholders of pharmaceutical industry include pharmaceutical companies, Healthcare Services Pricing Commission, Alternate Reimbursement Commission, Drug Reimbursement Commission, Medical and Economic Assessment Commission, Foreign Drug Medical and Economic Assessment Commission, clinicians and patients. The reimbursement level represents negotiations between pharmaceutical companies and SSI. The goal is access to market for pharmaceutical companies while deliver required drugs to patients for paying organization [7].

2. LITERATURE REVIEW

2.1. Reimbursement Process for Drugs

In 2009, Turkey imposed obligations to pharmaceutical companies to prepare reimbursement file folder and to present cost-effectiveness analysis about innovative drugs in this file folder for drugs which will be added to reimbursement coverage. This warranted pharmaceutical companies to prove cost-effectiveness of their products to public [16].

For inclusion to reimbursement coverage of a licensed product, the manufacturer should have to make an application to relevant divisions (secretariat) of SSI, General Directorate of General Health Insurance and Head of Drug and Pharmacy Department in accordance of Drug Application Guideline. The application file folder is controlled by secretariat and the pharmaceutical company is informed regarding failure to fulfillment, if present. Upon completion of failure to fulfillment, second application date is considered as valid application date. The literature and data in the application file folder are assessed by Medical and Economic Assessment Commission. After reaching a decision on the application file folder regarding clinical, technical and financial aspects, it is presented to Drug Reimbursement Commission. During assessment process, Drug Reimbursement Commission can refer to academicians or relevant specialist. After assessment process, Drug Reimbursement Commission presents the application file to SSI Presidential Executive Office and, if the application is granted, Health Application Communiqué is published in official gazette. The prescription conditions and reimbursement criteria for the agent decided to be included reimbursement coverage are added to 4A List for Drugs Reimbursed after publication in Health Application Communiqué [17]. The public price for reimbursable drugs is determined by application of obligatory public discount and special offers of pharmaceutical company. The discount rates and public prices are also included to 4A List for Drugs Reimbursed. The discount rates may vary according to original, generic and 20-years status of the drug. There are 9117 drugs in 4A List for Drugs Reimbursed upon 01.02.2019 [18].

The access to drugs not licensed in Turkey or licensed drugs not available in market due to several reasons are provided by Turkish Pharmacists' Association (TPA) and İbn-i Sina Health Social Security Center. The drug procurement is achieved according to The Guideline on Foreign Medicine Procurement and Use published by

Health Ministry and relevant regulations [18]. The inclusion to reimbursement coverage is decided by Foreign Drug Medical and Economic Assessment Commission. The commission evaluates the drug applications regarding medical effectiveness and cost-effectiveness and receives expert opinions; thereafter, it presents the drug application to Healthcare Services Pricing Commission. The drugs approved for reimbursement are published in Health Application Communiqué 4C Price List for Foreign Drug. The SSI does not provide reimbursement for drugs not included in the list [19]. There are 400 drugs in 4A List for Drugs Reimbursed upon 01.02.2019

2.2. Market Access Process

The manufacturers demanding to be included in reimbursement coverage should have to prove that their drugs offer additional benefit compared to available treatments and create value against its cost in order to be included to reimbursement coverage. In general, overall data indicate that practical clinical effectiveness and cost-effectiveness during registration process are not sufficient to accurately predict its effect on budget in real life. Even the payer organization reimbursed the cost of healthcare services at a known price; the equivocalness continues to exist about health production regarding the service. This equivocalness delays reimbursement decisions and patient's access to drugs due to insufficient data regarding effectiveness. Together with risk for not to be included, such delays have become a factor that discourages the industry from investing high-risk fields with low market potential (e.g. orphan drugs). This allowed development of formal arrangements to share financial risk of novel technologies between payers and manufacturers and their application for access of patients to novel drugs [11, 20].

Currently, it is of importance for healthcare industry to access market. Market access concept was first defined by World Trade Organization as opening market to trade, improving principle of translucency in international trade, reciprocity and lack of discrimination [21]. In the literature, market access is defined as introduction of good into market and opening of market to novel services and products by countries. However, there are important differences which differentiate healthcare services and products from other services and products. The World Health Organization (WHO) has emphasized that access to healthcare services is a human right. Thus, access to drug or a health product is also a human right [7]. In other words, market access is the entirety of processes that

ensures delivery of a product to all appropriate patients requiring the product in an inexpensive, rapid and sustained manner [22].

In general, market access involving registration, pricing and reimbursement processes, can be defined as the objective to achieve minimum limitation in reimbursement and maximum reimbursement for a healthcare service or product in a defined group of indication with optimum price. In particular, pricing and reimbursement are major barriers. It was seen that drug expenses could not be controlled sufficiently while aiming more equitable and translucent pricing process by international reference pricing system. It is thought that this may be due to fact that drug prices might have been constructed according to reference countries by pharmaceutical companies. In Turkey, pharmaceutical companies can demand maximum 100% of reference price for original drugs and maximum 60% of reference price for drugs without original formulations and those generic formulations [10].

The pricing is an important process. The drug prices have major impact on profitability of companies. In a previous study, it was concluded that 1% increase in the drug prices resulted in 8% increase in the profit [7].

Market access agreements are major importance for manufacturers regarding market penetration of novel products since higher price does not mean higher income. Either failure to inclusion into reimbursement coverage or not being recommended according to Health Technology Assessment will be great loss for manufacturer [23]. The Health Technology Assessment informs decision-making process about reimbursement coverage, price negotiations, and benefits and losses of novel drug relative to available treatment modalities [22]. High drug prices continue to create pressure in improving assurance of pharmaceutical companies about their products will worth additional expenses. To improve assurance and maintain investment incentives, pharmaceutical company should clarify uncertainties about whether the product is effective for consumers and payers [24].

In the perspective of reimbursement organization, inclusion of a product into reimbursement coverage will produce a financial burden and reimbursement organization should stay in the range of budget. Besides, it is needed to repay treatments with proven clinical effectiveness which ensures improvement in the health outcomes [21]. The clinical evidence are most important factors in this process. The cost, valuation and assessment can only be constructed on clinical outcomes. The clinical evidence should have to be presented in a comparative manner with standard care and benefit should have

to be defined based on the comparison. The reimbursement organization entails predictable patient outcomes and data regarding how many patients can be treated with the drug. The payers will feel safe about effects on budget as much as they have assurance regarding extent of patient population. If the drug is more beneficial for a certain group, it should be mentioned in the subgroup analyses. The reimbursement organization entails definition of eligible patient group for reimbursement [22].

The reimbursement organization generally executes a 4-step assessment process in order to control drug expenses and when making an investment that would achieve best health outcomes:

- The effectiveness of the drug is evaluated against alternative treatment by comparing 2 drugs in clinical trials [21].
- A comparison regarding drug effectiveness is performed between real life data and alternative treatments. This involves a process based on amount or level of reimbursement against health outcomes or costs, in which product performance is observed in a certain patient population [25].
- The cost-effectiveness of drug is determined.
- In the final step, it is assessed whether drug can be afforded by available budget. Even the treatment is considered as cost-effective, it will be impossible to afford when there is no ability to repay [21].

The time needed to market access has distinct implications for pharmaceutical company, clinicians, patient and reimbursement organization. The pharmaceutical company considers that the company is successful when it can achieve market access as rapid as possible. By this way, it aims to gain profit rapidly and to be able to invest new products. Clinicians desire to prescribe different treatment options to their patients. The patient demands to access novel technologies as soon as possible. In the perspective of reimbursement organization, the organization should ensure access to a drug by patient requiring the drug while considering overall drug expenses, its percentage in healthcare expenses, market balance and sustainability. For decision-making, evidence should be presented in convincing and rapid manner; uncertainties should be tolerable; and the organization should be assured about value of drug [22]. In the perspective of reimbursement organization, there are concerns whether promising, expensive and novel technologies will offer their gains in the real-world conditions and whether they have best values. For many reimbursement organizations, value is a function of clinical

effectiveness and cost-effectiveness. However, the value concept is not a simple quantitative assessment, requiring several decisions and assumptions. The controlled clinical trials should be generalized to provide predictions about clinical effectiveness in real life and to quantity life-long cost of disease [26].

Although perception of value changes over time, it has been one of the major issues in pharmaceutical field and in other fields. The reduction in the ability of pay exerts pressure due to economic compression. This resulted in need to prove that benefit is worth to buy. The prices should represent the value but it is not always simple to express value in figures [22].

The value-based pricing is a kind of pricing based on calculated or estimated value relying clinical benefit or benefit in the perspective of reimbursement organization and including prices of other available alternatives. In other words, in this pricing type, health benefits offered by inclusion of novel product into reimbursement coverage is not less than health benefits disclaimed as a result of abolishing other healthcare services. Although value-based pricing does not involve cost analysis, it is estimated through perception of value of payers.

In Turkey, this issue was first brought forward in the meeting "Novel Approaches Market Access in Drugs" assembled by SSI and Turkish Drug and Medical Device Organization in 2011 [27]. The regulations about Alternative Reimbursement Commission were implemented in February, 10 2016. The drug purchase through alternative reimbursement method was started by February, 10 2016. Market access arrangements have been implemented in many countries including Belgium, Germany, Italy, Netherlands, Portugal, Sweden, United Kingdom, Spain, USA, Australia, Canada, Estonia, Hungary, Latvia, Serbia and Denmark since early 2000s.

Given the fact that Turkey will be the most rapidly aging population among OECD countries until 2050, it should be suggested this will be challenging for public but an opportunity for pharmaceutical industry. The burden of healthcare expenses caused by aging population is extremely critical. In previous studies, it was seen that more than half of healthcare expenses of an individual was spent after retirement. Thus, one should conveniently suggest that market access will become more important in the future [16].

Based on alternative reimbursement legislation implemented in 2016, agreements between SSI and pharmaceutical companies can be concluded. The process is defined in the legislation as follows:

- The pharmaceutical companies can apply alternative reimbursement,
- The applications are assessed by SSI Vice President and General Directorate of SSI,
- If application is approved a work group is constructed under non-disclosure agreement,
- The work group assesses application and relevant product regarding medical and economical manner,
- If the assessment process is considered as positive, the pharmaceutical company is invited for negotiation by General Directorate of General Healthcare Services,
- Draft agreement is signed in case of positive negotiations,
- The agreement is signed by SSI Vice President and General Directorate of General Healthcare Services and presented to members of commission,
- In case of positive consideration of commission, the agreement is simultaneously signed by representative of pharmaceutical company and SSI President or Vice President,
- The decisions of Alternative Reimbursement Commission accepted and signed are accomplished by Healthcare Services Pricing Commission and implemented after publication in formal gazette [15].

In the market access, the key point is to make their services sustainable and to achieve commercial success for pharmaceutical companies. However, for public, it is important to provide successful healthcare services; to preserve role of drugs in the disease management in an appropriate manner; to ensure access and equity; and to support R&D and production opportunities in the country with an appropriate construct. It is impossible to execute such processes independent from clinicians who are primary proponent of drug, patients who are consumer of drug and healthcare providers. The clinicians should have to access evidence-based procedures as an option and access to treatment would not become a burden for patients and healthcare providers [22].

The market access arrangement is a form of guarantee to pharmaceutical company for novel and costly products. The guarantees are used when asymmetrical data exist about a product [24]. The market access arrangements can be considered as risk sharing phenomenon for both manufacturer and reimbursement organization. The market access arrangements will remove uncertainties for either party [7].

The market access arrangements can be in different forms such as price-volume agreements, outcome-guaranteed programs, and evidence-development schemes. These

agreements can be defined with terms of "risk sharing arrangement", "performance-based agreements", "patient access programs" and "managed entry agreements" [28].

2.3. Risk-Sharing Agreements

Traditional reimbursement decisions can be classified under 3 categories including "yes", "no" and "yes with limitation". Reimbursement organizations increasingly adopt innovative reimbursement approaches to address escalation between bankrolling of expensive technologies and getting money's worth. The agreement models between manufacturers introducing novel technologies are observation of real use or performance in a clearly defined patient population and drawing conclusion regarding reimbursement level in some occasions. Either party shares risk if the technology does not fit to predefined expectation, use or effect on budget [26].

In recent years, healthcare budgets have been increased more than inflation in order to afford demands and improve quality of care. However, such increases are likely to be reduced actually by more translucent processes in order to prioritizing more strict productivity goals, apparent improvements in the quality of care and technologies that may present best value [26].

Risk-sharing agreement is an arrangement between manufacturer and payment organization that ensures access/reimbursement to a conditional health technology. These arrangements can use various mechanisms to remove uncertainties about performance of technologies or achieve their maximal use or to limit their effects on budget or manage adaptation of technologies. Basically, risk-sharing agreements call pharmaceutical company to risk price of drug. Both payment organization and company anticipate that drug will exert a certain effect on the patient. However, if the anticipation is not realized, the company may lose all or a part of income. The risk-sharing agreements are not novel concept, which have been used for decades worldwide. In recent years, the interest on this issue and number of countries using such agreements have been increased remarkably. The risk-sharing agreements are being used in specific types based on local conditions of the country [24, 29].

The outcome-based risk-sharing agreements are seen as major advance in reimbursement strategies of reimbursement organization in middle-income countries. Risk-sharing agreement helps to decrease medical uncertainties in coverage decisions for innovative health technologies. However, they may blunt translucency of drug pricing

and reimbursement. In conclusion, actual price per patient can only be estimated retrospectively. Thus, risk-sharing agreements can be interpreted as special, collusive pricing arrangement forms to facilitate differing pricing in middle-income countries [30].

There is an equality of overall income for pharmaceutical companies and of overall cost, Price x Volume (number of patient), for reimbursement organization. As a result of this equality, price and reimbursement condition are of importance for either party [16].

Table 1: Advantages and disadvantages of risk-sharing agreements in different perspectives

Parties	Advantages	Disadvantages
Manufacturer	➢ Marker access for promising technologies ➢ Best product performance by targeted use	➢ Cost/bureaucracy required for execution of agreement ➢ Refund/discount in case of failure to achieve predefined outcomes ➢ Restricted access when budget limits are reached ➢ Clinical effectiveness of a technology in real world can be compared with effectiveness of comparators
Payer	➢ Provision of technology as it shows its value ➢ Providing early access for patients and risk sharing with manufacturer if product failed to show predefined performance ➢ Effects of limit on overall budget ➢ Evidence-based agreement to reveal uncertainties	➢ Cost/bureaucracy required for execution of agreement ➢ Increase in non-transparent plans ➢ Management of multiple models by payer ➢ Need for withdrawal of agreement at the end of agreement duration (Withdrawal is challenging during practice)
Patient **Community**	➢ Access to promising technologies, more options and ensuring possible treatment only ➢ Promoting investment to innovation	➢ Barriers against participation to risk-sharing agreement ➢ Risk for achieving benefits expected ➢ Potential withdrawal of technology at the end of agreement ➢ Data protection issues ➢ More strong studies will not be performed

* Klemp et all, 2011

There are two primary way to address uncertainty regarding clinical effectiveness and/or cost-effectiveness. First way is provision of reimbursement for a limited time period in which additional evidence will be collected about drug effectiveness and updating reimbursement decision based on novel outcomes about cost-effectiveness. This model is being used in Netherlands, Sweden and Portugal. Second is deflation of price or limiting its use; thus, cost-effectiveness can be improved due to lower costs. In UK, discount is widely used as a part of patient-access plans while Italy uses combination of discount, outcome-based reimbursement and conditional treatment to improve cost-effectiveness. However, this option does not address major uncertainty in cost-effectiveness if it is not associated with data collection about updating coverage decision [28].

The risk-sharing agreements can be classified in two main categories including finance-based models and outcome/performance-based models [31]. The decision about which model will be implemented should be based requirements of payer and infrastructure of country. In general, outcome/performance-based agreements are used if there is a clinical uncertainty while finance-based agreements if there is uncertainty about budget [11].

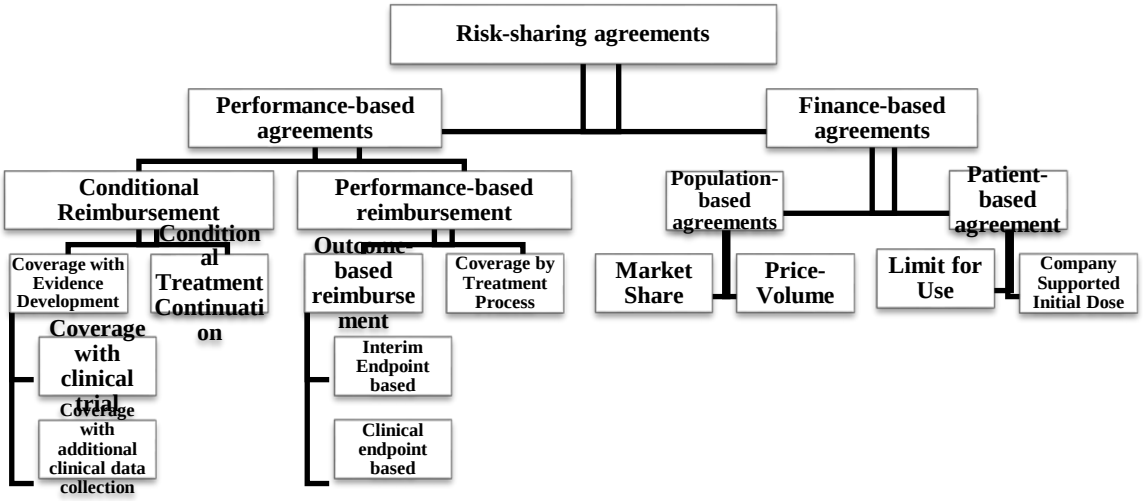

Figure 1: Alternative reimbursement models/risk-sharing agreements*

*Carlson et all, 2010

2.4. Performance-Based Agreements

Performance-based agreements are defined as arrangements between reimbursement organization ad manufacturers of medicinal products, in which price, level and characteristics of reimbursement depend on future clinical and interim analyses about quality of life or lifetime of patient. They arise from desire to provide access novel and potentially beneficial health technologies under remarkable uncertainty and cost pressure [31].

Performance-based agreements generally depend on, mostly clinical, predefined outcomes or new evidence. They are arrangements that regulate reimbursement according to predefined health outcomes of a product on a certain patient population during a certain period. They are generally monitored in the light of data obtained during the period in which drug is in use. Performance-based agreements support reasonable drug use in addition to aiding management of effect on budget and consuming cost-effective treatment [14].

Performance-based models involve plans that monitor drug performance in a certain patient population during a predefined period and are reimbursement coverage is determined according to health and cost outcomes obtained for drug.

In the market access process of novel drugs, there are some uncertainties regarding clinical and economical performance on the real-world conditions (effectiveness relative to standard care, number and characteristics of patients, ratio of responders in the real-life). The performance-based models offer a mechanism that allows use of drug within healthcare system as well reduction of uncertainties through more investment about evidence collection. In these models, an agreement is made between payer and company in order to implement a program for evidence/data collection. The program is either started or demanded by payer. By this way, it is aimed to reduce uncertainties regarding long-term effectiveness and cost-effectiveness of drug. Data collection can be performed either in a certain patient group/population or in the basis of patient. The results from data collection program can be apparently linked to drug price, reimbursement and/or income based on predefined rules or can be used as an option to reassess reimbursement coverage, price or income in the future. In some cases, reimbursement of drug is directly linked to performance of a certain patient [11].

2.5. Conditional Reimbursement

The conditional reimbursement is a model preferred to medicinal products which have available data or real world data insufficient for reimbursement decision. Such agreements offer chance to produce real world data for both reimbursement organization and pharmaceutical companies while prevent time-wasting in the market access for pharmaceutical companies. This is the most effective reimbursement model for budget control and prioritization [14].

Reimbursement level should not essentially account for 100% of purchase cost. These schemes include paying a part of drug cost spent by manufacturer when the drug included to conditional reimbursement could not achieved desired outcome in the eligible population and had negative health outcome. Briefly, conditional reimbursement programs can be defined as returning money spent for treatment by manufacturer when the patient could not achieve a certain goal [32].

The conditional reimbursement models are classified into two subgroups including "Coverage with Evidence Development" and "Conditional Treatment Continuation".

2.6. Coverage with Evidence Development

Coverage with evidence development involves inclusion to reimbursement cover of a technology or a drug warranting data collection via clinical trial or registries in order to determine effectiveness of a promising technology with participation of manufacturer. It is aimed to use data produced by trials or registries as a foundation for decision-making process of reimbursement cover in the future. It is determined whether a treatment is reasonable and necessary. In addition, it also aims to develop and support learning-based healthcare system. It has the advantage of providing a mechanism fulfilling requirement of evidence development for promising but not proven technologies in order to early introduction into clinical use. However, it also carries risk since it may not distinguish promising and premature technologies [33]. Coverage with evidence development is classified into 2 groups.

2.6.1. Coverage with Evidence Development

It involves inclusion of reimbursement cover by participation of manufacturer into clinical trial on the product without clearly proven effectiveness. In some countries, reimbursement cover is expanded when clinical trials proved effectiveness of treatment [14].

2.6.2. Coverage with additional data collection

When sufficient clinical data is lacking, reimbursement organizations include the product into reimbursement cover by subjecting to collection of additional clinical data. The agreement is made when the manufacturer accepts providing additional data regarding use in clinical practice and long-term effects on morbidity and mortality. Agreements based on coverage with additional data collection have been used since 2000s [14, 32].

2.7. Conditional Treatment Continuation

It works as inclusion of reimbursement cover for only treatment continuation in patients who achieved clinical effects targeted. In addition, such programs can involve complete or partial reimbursement for patients who could not achieve clinical effect targeted. In other words, it is a model where payer provides temporary finance to ensure data collection in order to clarify uncertainties about reimbursement decision. The disadvantage of this model is that the drug fails to demonstrate benefits proven in clinical trials in the real life due to errors in patient selection. Thus, eligibility criteria should be clearly defined to prevent such failure. For instance, in UK, the manufacturer pays out expenses as cash or product supply for the patient who did not respond to 4-weeks bortezomib treatment for multiple myeloma; however, responders are entitled for 4 additional cycles of treatment [14, 32, 34].

2.8. Performance-Based Reimbursement

The schemes in which level of reimbursement for products in the coverage linked to measurement of clinical outcomes are defined as performance-based reimbursement

[31]. It relies on reimbursement depending on only clinical outcomes in real life conditions. Pharmaceutical company accepted to supply certain amount of product without payment based on data in clinical trials. At the end of process, the drug is included to coverage for patient who gained benefit while different treatment options are sought for the patient without any benefit [14].

Performance-based reimbursement is classified into 2 categories as "Outcome-Based Reimbursement " and "Coverage by Treatment Process".

2.8.1. Outcome-Based Reimbursement

It involves refund or discount to reimbursement organization for the patient group who did not benefit from the drug included to reimbursement coverage. It is a model where the price is directly linked to a certain outcome in each patient. Based on the agreement, certain part of expenses for the patient who did not respond to treatment in the analyses at interim endpoint or clinical endpoint is refunded to reimbursement organization [14, 32].

2.8.2. Coverage by Treatment Process

It is based on reimbursement according to clinical decision-making and treatment models. In such schemes, reimbursement requirement is selection of patients by pharmaceutical company via biological markers such as genetic testing in accordance to clinical guidelines [14].

2.9. Finance-Based Agreements

To control drug budget, payers offer financial risk-sharing agreement to companies for novel drugs in increasing number of countries in order to manage their potential additional payments to companies [11]. Such agreements are used to manage financial risks arising from general use or uncertainties on prediction of costs or to reduce payment risk arising from drug use not included in restricted list (or inexpensive) [35]. Finance-based agreements generally rely on discount, influencing on net price. There is no need to collect patient data as the objective is to remove financial uncertainty rather than proving effectiveness [36].

Since 2000, finance-based agreements have been intensively employed in many European countries. In particular, it is the most common model in Italy. In our country, price-volume agreements are being used in recent years in order to reduce uncertainties caused by financial performance of novel molecules and public expenses [36].

2.10. Patient-Based Agreements

The models of patient-based agreement are characterized by different cost-effective prices for a certain technology in an individual patient. However, this is not achieved by linking prices to treatment factors rather than correlating outcomes to outcome measures.

2.11. Company-Supported Initial Dose

These are agreement models where the expenses of initial treatment period are funded by the pharmaceutical company regardless of failure or success and overall cost is reduced for reimbursement organization. It involves patient who received a technology for a price differing from listed price during initial period of treatment. Then, if a patient maintains treatment following a certain number of sessions or time period, price listed has become valid. Unlike conditional treatment continuation model, there is no consensus that the drug will retain in coverage if patients achieve effect targeted. For instance, in renal cell carcinoma, first sunitinib cycle is free for all patients in UK [32, 36].

2.12. Individual Limit for Use

In this model, also termed as individual volume, overall drug expense per patient is predefined by reimbursement organization. If it is decided that the patient requires further treatment after predefined treatment duration, a part or all of amount exceeding the limit is funded by manufacturer. These arrangements modify the risk of healthcare system at expense of cost of patient who received treatment more than predefined threshold [32].

2.13. Population-based Agreements

Population-based agreements are characterized by efficient price determined at the level of healthcare system rather than individual level.

2.14. Price-based agreements

Price modifications include discount as a result of negotiations on list price per box between manufacturer and buyer. However, such agreements are limited as a result of fact that drug pricing in a country is correlated to drug price in other country associated with global reference pricing. Thus, discount is generally classified and not published due concerns of companies regarding price attrition of their products. The model long has been used in our country and is also employed in 21 European countries [32, 37].

2.15. Price-Volume Agreements

These models are used against risk for exceeding number of patients predicted with unexpected increase in drug expenses after approval of market access for a product. The pharmaceutical company gives a discount at a certain rate for or refund exceeding amount to reimbursement organization when number of patient or box predicted is exceed. It is critical to monitor drug surveillance in the execution of this model [36]. In the model termed as budget-effect model, the price can be reduced to the price of the drug replaced when baseline list price of a drug is exceeded a predefined threshold that is considered to represent population size within volume of utilization [38, 39].

3. MATERIALS and METHODS

As a result of wide use of increasing market access agreements in recent years, market access agreements and processes have become one of the important topics for both companies providing healthcare services and health technologies and reimbursement organizations. Upon implementation of relevant legislations in 2016, market access agreements became feasible in Turkey. In our study, it was aimed to evaluate and report drug-based market access agreements performed in accordance to relevant legislations published in 2016.

3.1. Data Set

We used open, published data for our analyses. Firstly, a general literature search was conducted about alternative reimbursement models in National Thesis Center, Google Academics and Google Books databases by using keywords below: "alternative reimbursement ", "market access", "market access agreement", "risk-sharing agreement", "managed entry agreement", and "pharmaceutical market access"

In addition to literature search, relevant legislations, formal publications and reports were also screened. To evaluate actions for relevant legislations since 2016 and data, we used formal websites of SSI, TITCK, official gazette, Health Ministry, Association of Research-Based Pharmaceutical Companies (AIFD) Pharmaceutical Manufacturer Association of Turkey (IEIS) and Turkish Pharmacists' Association (TPA).

- SGK : http://www.sgk.gov.tr/wps/portal/sgk/tr
- TİTCK : https://www.titck.gov.tr/
- Official gazette: http://www.resmigazete.gov.tr/
- Health Ministry: https://www.saglik.gov.tr/
- Association of Research-Based Pharmaceutical Companies: https://www.aifd.org.tr/
- Pharmaceutical Manufacturer Association of Turkey : http://www.ieis.org.tr/ieis/tr/
- TPA : https://www.teb.org.tr/

Data were extracted from up-to-date TITCK List for Foreign Medicine, SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine at 01.02.2019.

Finally, official gazette issues published between 10.02.2016 and 02.02.2019 were reviewed, including Healthcare Services Pricing Commission (HSPC) (last access: 21.05.2019).

3.2. Data Analysis

Data extracted were transferred to Windows Office Excel. Descriptive analyses were performed using data extracted:

- Drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,
- Distribution of drugs (per year) included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,
- Reference prices for drugs included to SSI Supplementary lists of Supplementary 4A List for Drugs Reimbursed,
- Reference prices in Turkish Lira for drugs included to SSI Supplementary 4A List for Drugs Reimbursed were calculated according to "Periodic Euro Currency Employed for Drug Prices" published by Pharmaceutical Manufacturers Association of Turkey. The fixed exchange rate employed for drugs is 1 Euro= 3.4037 TL upon 14.02.2019.
- The distribution of prices for drugs included to SSI Supplementary 4A List for Drugs Reimbursed according to reference country.
- List prices on yearly basis for drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,
- Discount rates for drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,

- The ATC distribution of drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions
- Disease-based distribution of drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions
- Pharmaceutical company-based distribution of drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,
- Original product- and generic-product distribution of drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,
- Reimbursement restriction-based distribution of drugs included to SSI Supplementary 4A List for Drugs Reimbursed and Supplementary 4C Price List for Foreign Medicine by Alternative reimbursement in HSPC decisions,

3.3. Expert Opinion and Assesment

Outcomes from data transferred to Windows Office Excel and underwent descriptive analyses were assessed by Dr. Güvenç Koçkaya and Dr. Gülpembe Oğuzhan studying in market access and health economics.

Data, descriptive analyses and expert opinion were reported in attempt to provide a basis for further analyses.

4. RESULTS

The aim of Alternative Reimbursement Regulations implemented at February, 10 2016 was documented as *"The objective is, other than ancestors, principles and regulations, to regulate rules and procedures regarding determination of reimbursement models which are created to encourage domestic production or market availability of products exported or those not produced or not available in Turkey which are currently or will be include, in reimbursement coverage by adding product and service groups or modifying regulations in required fields based on economic and medical benefits."*. For this purpose Alternative Reimbursement decisions ruled by Healthcare Services Pricing Commission are published in official gazette.

In Turkey, the first products received alternative reimbursement approval by HSPC decisions at 18.06.2016 were those used in the treatment of Hepatitis C. The discount rates for these products were not published and classified discount was introduced. It was the first time that the products were included to HAC Supplementary 4A List for Drugs Reimbursed by assessment of Alternative Reimbursement Commission via classified discount rates [11].

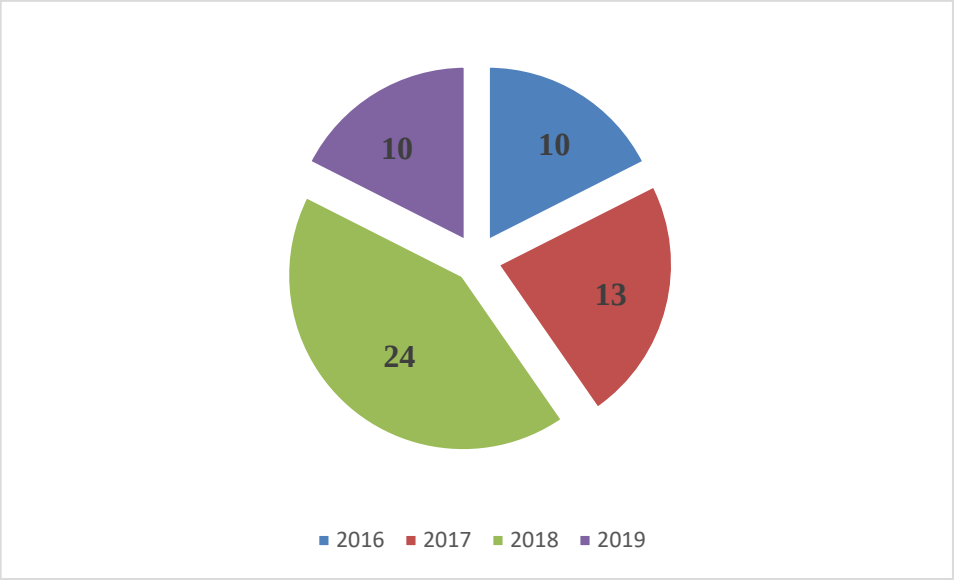

Figure 2: Drugs included to reimbursement coverage by alternative reimbursement methods on yearly basis

Currently, there are 57 drugs in the process of Alternative Reimbursement (latest access: 21.05.2019). Of 57 drugs, 10 were included to alternative reimbursement coverage in 2016 while 13 in 2017, 24 in 2018 and 10 in 2019. There are 39

pharmaceutical companies having access to Turkish market via alternative reimbursement methods.

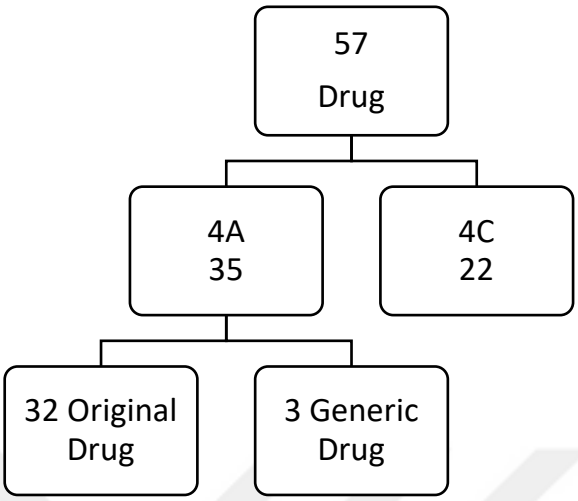

Figure 3: Distribution of drugs in alternative reimbursement coverage according to HAC list

As seen in Figure 3, of 57 drugs purchased by alternative reimbursement agreements, 35 were included to 4A List for Drugs reimbursed while 22 were included to 4C Price List for Foreign Medicine. Of drugs included to 4A List for Drugs Reimbursed, 32 are original while 3 are generic drugs. It is seen that vast majority of drugs included to reimbursement coverage are original products. There is no restriction for 24 drugs in 4A List for Drugs Reimbursed and for 18 drugs in 4C Price List for Foreign Medicine.

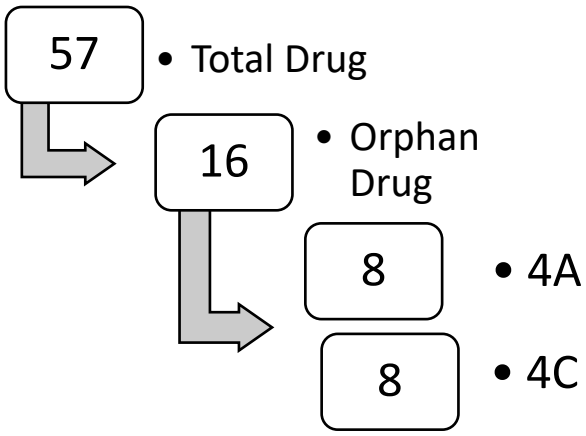

Figure 4: Distribution of orphan drugs in alternative reimbursement coverage

As seen Figure 4, there are 16 orphan drugs in reimbursement coverage. Of these, 8 are in 4A List for Drug Reimbursed while 8 are in 4C Price List for Foreign Medicine.

Table 2: Distribution of drugs in reimbursement coverage according to ATC

ATC Codes		Total	4A	4C
L	Anti-neoplastic and immunomodulatory agents	26	21	5
A	Alimentary tract and metabolism	10	3	7
J	Anti-infective agents for systemic use	5	5	-
M	Musculoskeletal system	4	1	3
N	Nervous system	3	2	1
V	Various	3	1	2
D	Dermatologic agents	2	1	1
R	Respiratory system	1	1	-
C	Cardiovascular system	1	-	1
B	Blood and blood forming organs	1	-	1
N/A		1	-	1
Total		**57**	**35**	**22**

Table 2 presents distribution of drugs in reimbursement coverage according to ATC. As seen, largest ATC group is L-Anti-neoplastic and Immunomodulator agents. The group is generally associated with cancer and immune system disorders.

Table 3: Distribution drugs in alternative reimbursement coverage according to disorders

DISEASES	Number of products
Malignant Melanoma	5
Hepatitis C	4
Breast cancer	3
Multiple Sclerosis	3
Non-small Cell Lung Cancer	3
Multiple Myeloma and Plasma Cell Disorders (rare disease)	3
Phenylketonuria (rare disease)	2
MPS (Maroteaux-Lamy) Type VI (rare disease)	1
Chronic Lymphocytic Leukemia	1
Diabetic Foot Ulcer	1
Leptin deficiency (rare disease)	1
Respiratory inflammation	1
Disorders of Biliary Acid Zellweger Spectrum Disorders (rare disease)	1
Duchenne Muscular Dystrophy (DMD) (rare disease)	1
Osteosarcoma	1

Ulcerative Colitis and Crohn Disease	1
Morquio syndrome (rare disease)	1
Spinal Muscular Atrophy (SMA) (rare disease)	1
Gaucher Disease (rare disease)	1
Acute Lymphocytic Leukemia (ALL)	1
Paroxysmal Nocturnal Hemoglobinuria and Atypical Hemolytic-Uremic Syndrome (rare drug)	1
Parkinson Disease	1
Disorders of Urea Cycle Metabolism	1
Cerebral Palsy	1
Malignant Neoplasm	1
Wilson's Disease	1
Chronic Hyperuricemia	1
Chronic Lymphocytic Leukemia, Mantle Cell Lymphoma (rare disease)	1
Acute and Chronic Leukemia (rare disease)	1
AIDS, with Cytomegalovirus (CMV) Retinitis	1
Brain Tumors, Multiple Myeloma, Hodgkin's Disease, Non-Hodgkin Lymphoma	1
Medullary Thyroid Cancer (rare disease)	1
Eczema	1
Hunter Syndrome	1
Leishmaniasis, Infection with Free Living Amoeba	1
Hypertriglyceridemia	1
Cancer, Wilson's Disease, Disorder of Copper Metabolism: Seropositive Rheumatoid Arthritis, Rheumatoid Arthritis; other; Juvenile Arthritis, Amino Acid Transfer	1
Congenital Metabolic and Hereditary Diseases	1
MNGIE (Mitochondrial Neurogastrointestinal Encephalomyelopathy), Congenital Metabolic and Hereditary Diseases	1
Intocixation by Organophosphorus Pesticides and Chemical Compunds	1

As seen in Table 3, the oncology agents comprise majority of drugs in reimbursement coverage by decision of Alternative Reimbursement Commission when agents are classified based on disease. It should be suggested that purchasing anti-cancer agents by alternative reimbursement will be in favor of public interest due to increasing cancer incidence and higher costs. In addition it is seen that drugs for Hepatitis C and Multiple Sclerosis are also purchased intensively. This may be due to the fact that extremely higher drug costs might have facilitated inclusion of drugs into reimbursement coverage via agreements between pharmaceutical companies and public. Overall, it is

seen that use of alternative reimbursement models has become increasingly common in drugs with high costs.

When assessed according to disorders, it is seen that there are 16 products related to 13 rare diseases. When agents included to reimbursement coverage for rare diseases are assessed, it is shown that there are 3 products for Multiple Myeloma-Plasma Cell Disorders and 2 products for Phenylketonuria in reimbursement coverage.

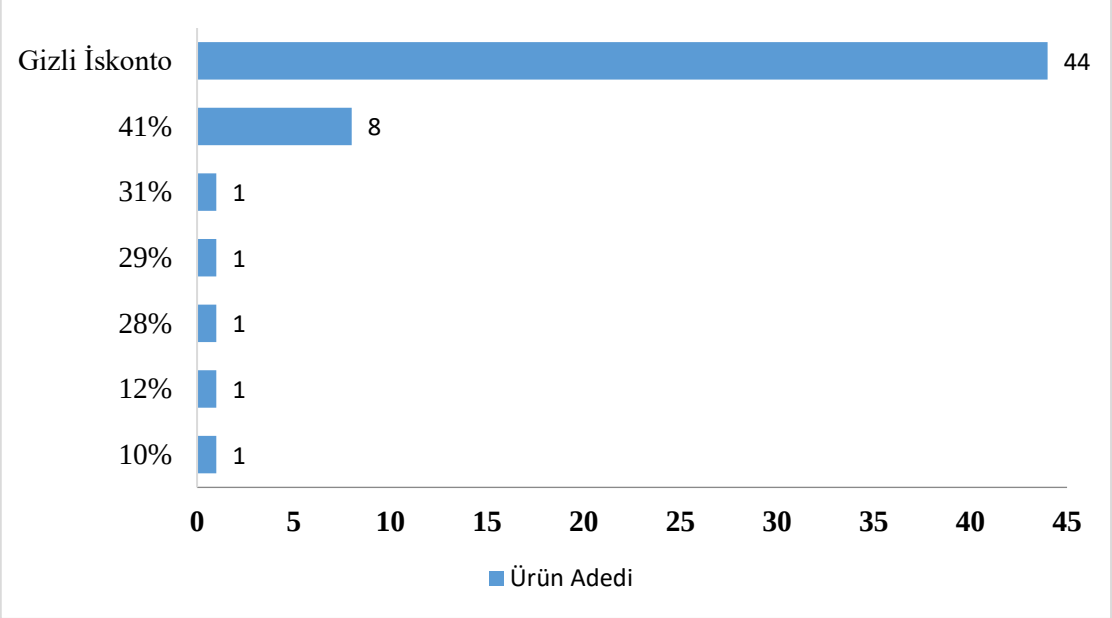

Figure 5: Public discount rates for drugs in alternative reimbursement coverage

As seen in Figure 5, public discount rates are not disclosed for 44 products (77.19%). The classified discount model is applied to these products. The discount rates are 41% in 14.03%, 31% in 1.75%, 29% in 1.75%, 28% in 1.75%, 13% in 1.75%) and 10% in 1.75% of 57 products. Due to reference pricing employed in our country, effects of changes in other countries will result in higher cost for public. To ensure protection against this issue, classified discount is employed between company and reimbursement organization and public prices aren't disclosed.

Mean discount rate is found as 33.69% for products in which prices are disclosed. Of 13 products with disclosed price, discount rate from list price is 41% in 8 products. All 13 products are included to 4A List for Drugs Reimbursed and it is possible to obtain public price and their cost for SSI. Although the prices of these agents vary from 9.04 TL (Oxofen 2 mg/ml suspension, 150 ml; drug substance: fenspiride) to 16.226 TL

(Imbruvica, 140 mg 120 capsules; drug substance: ibrutinib), mean public price is 3839.67 TL.

Table 4: Mean reference price and list prices for drugs in alternative reimbursement coverage

		Overall	**2016**	**2017**	**2018**	**2019**
Mean Reference Price	**Mean**	3.167,61 €	5.705,61 €	1.309,47 €	3.262,05 €	40,50 €
Reference Price Estimated According to Mean Fixed Exchange Rate	**Mean**	10.781,60 TL	19.420,19 TL	4.209,58 TL	11.103,04 TL	137.85 TL
Mean list price	**Mean**	2.856,58 €	2.820,79 €	7.994,18 €	1.464,45 €	1.805,92 €
• **4A Mean list price**	**Mean**	1.572,11 €	3.017,87 €	652.37 €	1.560.74 €	59,07 €
• **4A Mean list price**	**Mean**	10.480,72 TL	20.119,10 TL	4.349,12 TL	10.404,96 TL	393,77 TL
• **4C Mean list price**	**Mean**	5.542,28 €	2.360,94 €	24.513,25 €	999,05 €	1.200,01 €

*Price lists (TL) for drugs in 4A List for Drugs Reimbursed published by SSI, Price lists (Euro and Dollar) for drugs in 4C Price List for Foreign Medicine. For comparison, exchange rate at 06.05.2019 (1 Euro= 6.67 TL) and exchange rate (1 Euro= 1.11 Dollar) for price lists in 4C Price List for Foreign Medicine were used.

*Reference Prices include 4A List for Drugs Reimbursed

*Reference prices for drugs in 4A List for Drugs Reimbursed are presented as Euro. The prices in TL were calculated according to Periodic Euro Exchange Rate for Drug Prices published by Pharmaceutical Manufacturers Association of Turkey. Fixed exchange rate applied by 14.02.2019 is 3.4037

When mean reference prices are assessed for products purchased via alternative reimbursement methods, mean price was found as 3167 Euro. When mean price is assessed on yearly basis, it was seen that mean price was extremely high in 2016. This may due to fact that price was >8000 Euro in 3 of 7 products purchased in 2016. In 2017, 9 products were included to reimbursement coverage, 5 of which had a price <1000 Euro. In 2018, 18 drugs and 29 products were included to reimbursement coverage, 12 of which had a price of 3000-8000 Euro. In 2019, only one product (Contration; drug substance: pyralidoxim methyl sulfate) with a reference price of 40.50 Euro was added to 4A List of Drugs Reimbursed.

When list prices were assessed, it was seen that highest mean price was noted in 2017. This may be due to fact that Spinraza (drug substance: nusinersen) included to

reimbursement coverage by adding to 4C Price List for Foreign Medicine in 2017 was 90,000 Euro. In 2017, 9 products were included to reimbursement coverage by adding to 4A List for Drugs Reimbursed, 4 of which had a list price <1000 Euro; thus, mean list price was low. In 2019, only one product ((Contration; drug substance: pyralidoxim methyl sulfate)) with a list price of 59.07 Euro was added to 4A List for Drugs Reimbursed.

Table 5: Pharmaceutical companies with access to Turkish Market and Reference Countries

Pharmaceutical Company	**Reference Country**	**Number of Products**
Roche	Switzerland	5
Abbvie	Greece	3
Biomarin	Portugal	3
Gilead	Greece	3
Takeda	Germany	3
BMS	Puerto Rico	2
Gen İlaç	Germany	2
Novartis	Switzerland	2
Amgen	Netherland	2
Astrazeneca	France	2
Konsina İlaç	United States	2
Celgene	Switzerland	1
UFSA	France	1
Johnson & Johnson	Greece	1
Hasbiotech	Cuba	1
Aegerion	-	1
Gensu Pharma	Italy	1
Retrophin	-	1
PTC Therapeutics	-	1
TEVA	Israel	1
Biogen	-	1
Pfizer	United States	1
TRPharm	Portugal	1
Alexion	-	1
Sumitomo Dainippon Pharma	Japan	1
Pharmaxis	Australia	1
EVER Pharma	Austria	1
Merck Sharp & Dohme	United States	1
Taj Pharma	India	1
Exelixis	United States	1

Solvay Pharma	Belgium	1
GC Pharma	South Korea	1
Knight Therapeutics	Canada	1
Heyl	Germany	1
Sanova Pharma	Austria	1
PIAM	Italy	1
Nestle Health Science	Australia	1
Keymen	France	1
Other	-	1

As seen in Table 5, there are 39 pharmaceutical companies having access to Turkish market. Roche (5 drugs) and Abbvie, Biomarin, Gliead and Takeda (3 drugs for each) are most commonly encountered pharmaceutical companies during alternative reimbursement process.

Table 6: Countries identified as reference for active market access in Turkey

	Total	**2016**	**2017**	**2018**	**2019**
Switzerland	9	1	3	5	
Greece	6	4	1	1	
Germany	5	1	3		1
United States	5			4	1
France	3			2	1
Italy	2		1		1
Portugal	2			2	
Australia	2			1	1
Austria	2			1	1
Netherlands	2			2	
Cuba	1	1			
Israel	1		1		
Puerto Rico	1			1	
Japan	1			1	
India	1				
Denmark	1			1	
Belgium	1				1
South Korea	1				1
Canada	1				1
Other	10	3	4	2	1
Total	**57**	**10**	**13**	**24**	**10**

Table 6 presents countries identified as reference in market access in Turkey. The Switzerland has high number of products since it country of origin for big pharmaceutical companies such as Roche and Novartis.

5. DISCUSSION and CONCLUSION

The increasing demand to healthcare over time due to rapid increase in healthcare expenses, elevated drug prices and aging population have been resulted in problems in the effective management of limited budget. Turkish drug market has reached to a value of 33 billion TL and 2.3 billion boxes in prior 12 months by March, 2019. This warranted taking measures for expenses to achieve a sustainable, effective, equitable and high quality healthcare system. Thus, public authorities implemented some programs to reach cautious decision regarding expenses of novel treatments and drugs [8].

By establishment of Alternative Reimbursement Commission in accordance with regulations published in 2016, it was aimed to control drug expenses and to deliver treatments with lesser cost through agreements between pharmaceutical companies and reimbursement organization. Such agreements are beneficial for both public and pharmaceutical companies. The most important way to access market is inclusion of product into reimbursement coverage. The pharmaceutical companies should have to prove that the product offered for inclusion to reimbursement coverage is effective in financial and clinical manner. Some products will have limited impact on budget since they are more cost-effective in certain subgroups although they have broad indications. There is an uncertainty for either party and agreements serve for risk-sharing between either party.

Since its implementation in 2016, there are 57 drugs included to reimbursement coverage by Alternative Reimbursement. Of 57 drugs, 10 were included to alternative reimbursement coverage in 2016 while 13 in 2017, 24 in 2018 and 10 in 2019. Again, of these drugs, 35 were included to 4A List for Drugs reimbursed while 22 were included to 4C Price List for Foreign Medicine. Sixteen of 57 are orphan drugs.

It is seen that 91.42% of drugs included to 4A List for Drugs Reimbursed are original agents. This indicates that there is a need to add novel and effective treatments into reimbursement coverage in our country. Sixty percent of drugs added to reimbursement coverage by alternative reimbursement are related with cancer and immune system disorders. When list prices are considered, it is seen that lowest price is 2.51 Euro while highest price is 7991.92 Euro with a mean price of 1572.108 Euro. The discount rate is classified in 22 products while mean discount rate is 33.69% in remaining 13 products. There is no restriction for reimbursement in 11 drugs while some patient-based restrictions in 24 of 35 drugs included to 4A List for Drugs Reimbursed.

When 4C Price List for Foreign Medicine is assessed, it is seen that 31.8% of 22 drugs are associated to digestive system and metabolism disorders. When list prices are assessed, it is seen that lowest price is 7.6 Euro while highest price is 90,000 Euro with a mean price of 5542.28 Euro. The wide difference between lowest and highest price can result in misleading mean price. The high mean price is due to Spinraza(12 mg/5 ml; 1x 5 vials), a drug used in SMA treatment, which has list price of 90,000 Euro. When it is excluded mean price is 1520.48 Euro. The discount rate is classified in all drugs in 4C Price List for Foreign Medicine. All agreements between reimbursement organization and pharmaceutical companies for drugs included to 4C Price List for Foreign Drugs are finance-based agreements.

It was found that mean list prices is 2856.58 Euro for drugs added to 4A List for Drugs Reimbursed and 4C Price List for Foreign Medicine by alternative reimbursement. The alternative reimbursement models are preferred for reimbursement of drugs with high cost.

There are 39 pharmaceutical companies having access to Turkish market by alternative r reimbursement model. Roche has highest number of product (5 products) in reimbursement coverage among 39 pharmaceutical companies.

Although there are 5 countries (Greece, Italy, Portugal, France, Spain) identified as source for reference pricing system, the lowest prices among countries importing the drug can be used as reference price. When reference countries for drugs added 4A List for Drugs Reimbursed are assessed, it is seen that Switzerland is most intensively used country; followed by Greece.

The fact that agreements between reimbursement organization and pharmaceutical companies are solely finance-based agreements facilitates implementation and follow-up; however, performance-based agreements can provide more data about clinical effectiveness of product and can develop evidence, resulting in more effective treatment at patient level. However, performance-based agreements are challenging in practice and require appropriate infrastructure.

In general, it should be suggested that agreements based on alternative reimbursement models are advantageous for both public and pharmaceutical companies. Although infrastructure is lacking in our country, there are deficiencies in legislations regarding alternative reimbursement. In recent years, pharmaceutical companies established relevant departments and promoted studies in this field. In particular, finance-based agreements are preferred for drugs with high cost. In the future, implementation of

performance-based agreements between public and pharmaceutical companies will help to resolve uncertainties about performance in real life. Appropriate infrastructure should be developed in our country.

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ANNEX I

CURRICULUM VITAE

Personal Informations

Name	Okan	**Surname**	Atalay
Place of Birth	Orhangazi	**Date of Birth**	01.03.1969
Nationality	Turkey	**TC ID Number**	37411058740
E-mail	okanatalay1@gmail.com	**Phone Number**	05332757737

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Master	Yeditepe University	Institute Of Health Sciences	2020
University	Uludag Universty	Veterinary Faculty	1991
High School			

Languages	Grades*
English	Upper intermediate

* 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)
Gov.Aff.Manager	Chiesi	2
Sales/Training / Gov.Aff.Manager	Servier	19
Medical delegate	Pfizer İlaç	3

Computer Skills

Program	Level*
Word, Excel, Power point	Good

* Excellent, good, average or basic