Orphan Drugs of Personalized Medicine in Bulgaria and Their Cost-Effectiveness

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Abstract

The orphan drugs development is related to the progress of personalized medicine. The relationship between them is based on a treatment tailored to personalized patient needs. Personalized medicine is defined as "providing the right patient with the right drug, at the right dose and at the right time", while the orphan drug is defined as "intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons in the United States" and no more than 10,000 people for the European Union. The main goal of the article is to study the approved orphan drugs in Bulgaria, determining how many of them are reimbursed by the NHIF and are cost-effective.

Keywords: Orphan drug; Personalized medicine; Cost-effectiveness

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Introduction

The orphan drugs development is related to the progress of personalized medicine. The relationship between them is based on a treatment tailored to personalized patient needs.

This is the reason that personalized medicine is defined as "providing the right patient with the right medicine, at the right dose and at the right time," (FDA, 2019; Abrahams, 2008; (Stoykova & Dimitrova-Koeva, 2019) while, today, the orphan medicine is defined as "intended to treat, prevent, or diagnose a rare disease that affects less than 200,000 people for the US and no more than 10,000 people for the EU. (National Organization for Rare Disorders,2020; Committee for Orphan Medicinal Products (COMP), 2000).

1. Thesis statement and literature review

The first use of the term "orphan" in the context of drugs was in the 1968 article by Dr. Harry Shirkey, published in The Journal of Pediatrics (Shirkey,1968). In the article, Dr. Harry Shirkey discusses that the study of the efficacy and safety of medicines for children is considered unprofitable by pharmaceutical manufacturers, and often children are also treated as patients with drugs for which there is no information for their side effects. As a result, the lack of research leads to the "orphaning" of certain diseases and makes them "orphans". This is the beginning of "orphan drug" term application and to other therapeutic areas for which no information was available. (Christensen & Chesney,2003; Sasinowski & Hull, 2015).

Fifteen years later, in 1983 the first orphan drug legislation is created in the United States with the Orphan Drug Act (ODA). The main goal of stimulating the development of drugs that treat rare diseases." (Nabhan et al., 2018) Today, the law is often considered one of the most successful health legislation enacted in the United States (Novas,2009; Mikami,2019).

The European regulation of orphan medicinal products was introduced by Regulation (EC) № 141/2000 adopted of the European Parliament on 16 December 1999. The legal framework was formally published in the Journal of the European Communities on 22 January 2000 (European Medicines Agency, 2020, Official Journal of the European Communities, 2000). According to, European Union legislation, rare diseases are any disease that affects less than 5 people per 10,000 in the European Union, or 246,000 patients who are part of the European space. The main aim of the article is to study the authorized orphan drugs in Bulgaria, determining how many of them are reimbursed by the NHIF and are cost-effective. (European Commission, 2020, European Medicines Agency, 2020, Enzmann et al., 2012, Stoykova-Valcheva,2020).

2. Methodology

The primary research is made and based on - content analysis, compilation and statistical methods for data processing, the secondary research is based on a literature review related to the

article topic. The article discusses and analyzes data for assessing the economic effectiveness of orphan drugs in Bulgaria.

3. Results and discussion

The literature discusses, that the development of orphan drugs is closely associated to the progress of personalized medicine. The connection between rare diseases and personalized medicine is their target in treatment tailored to the individual needs of the patient (Deuchars, 2020, Bulera, 2012).

The results of our study present that orphan drugs for personalized treatment worldwide are - 52 or 33.12% of the total number of personalized therapies (targeted therapies) with count – 157 or 67% (Stoykova-Valcheva,2020) (Figure 1).

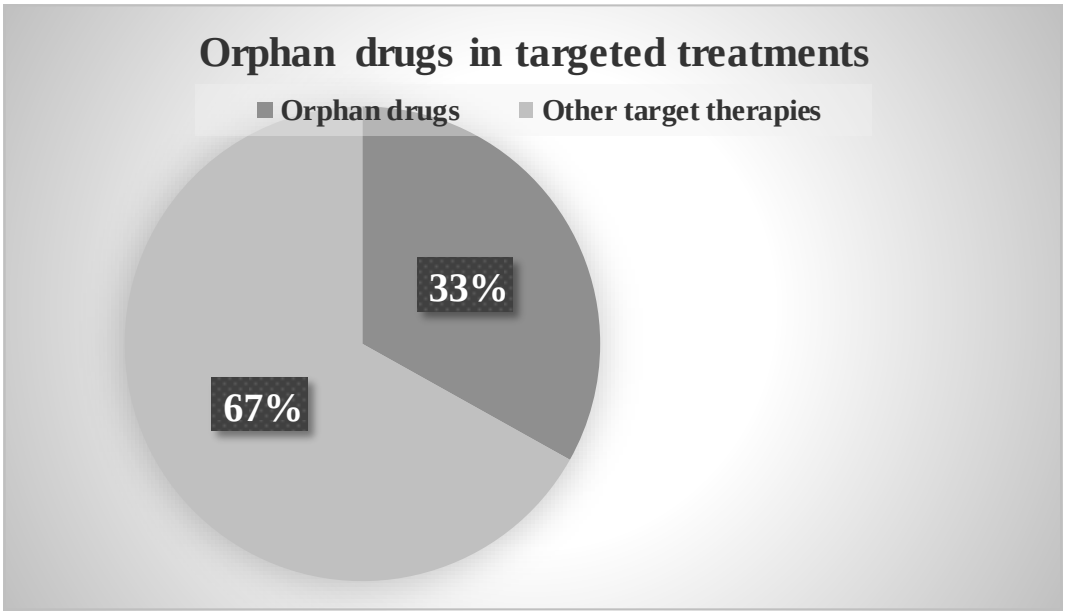

Figure 1. Orphan drugs in targeted treatments

As a result of our research, 52 are all approved orphan drugs worldwide, and 22 or 42.30% of them are approved for use in Bulgaria. In the last few years (2017-2020) there has been a significant increase in the permitted and reimbursed orphan drugs in Bulgaria. (Figure 2).

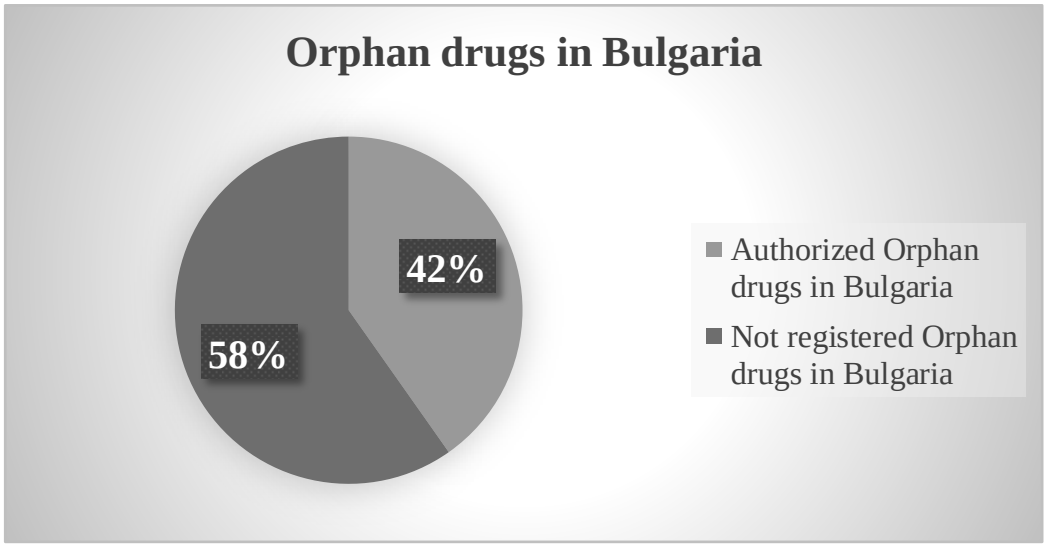

Figure 2. Orphan drugs in Bulgaria

The results of our study, based on NHIF data, identify 22 orphan drugs authorized for use in Bulgaria. Table 1., presents all therapies, with their The Anatomical Therapeutic Chemical code: (ATC Code) and International Nonproprietary Names (INN), besides, the Table 1., identifies which of these 22 orphan drugs are for target cancer treatment. The primary reason for this is that the most developed therapeutic area in personalized medicine is oncology. Nowadays, targeted therapies are presented in "Personalized Oncology" (Bode & Dong, 2017; (Stoykova-Valcheva,2020).

The enormous contribution of targeted cancer therapies is the targeted treatment of only cancer cells, as a result healthy cells are with minimal damage. In addition, personalized treatment has minimal side effects than standard methods of treatment (Krzyszczyk et al., 2019, Pierpont et al., 2018; Stoykova-Valcheva,2020).

The result of our research is that 82% or 18 counts of the orphan drugs in Bulgaria are for cancer treatment and 18% treat other therapeutic diseases. (Figure 3).

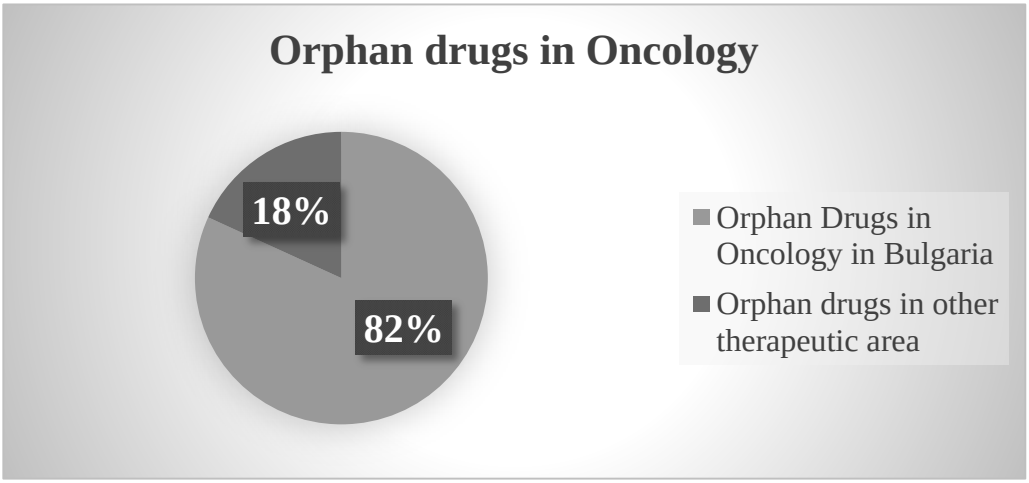

Figure 3. Orphan drugs in Oncology

Results of our research from the Table 1. are that 20 orphan drugs are reimbursed by The National Health Insurance Fund (NHIF) and only 2 drugs are not reimbursed by the NHIF, but are approved for use. (Figure 4).

Table 1. List of orphan drugs in Bulgaria

№	Orphan drug - Trade name	INN/ATC	Orphan drugs in Oncology	Reimbursed by the NHIF - Orphan drugs
1	Lynparza	Olaparib L01XX46	Oncology	Reimbursed
2	Vimizim	Elosulfase alfa A16AB12	Mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA)	Reimbursed
3	Cerdelga	Eliglustat A16AX10	Gaucher disease type 1 (GD1)	Reimbursed
4	Blincyto	Blinatumomab L01XC19	Oncology	Reimbursed
5	Alecensa	Alectinib L01XE36	Oncology	Reimbursed
6	Bavencio	Avelumab L01XC31	Oncology	Reimbursed
7	Rydapt	Midostaurin	Oncology	Reimbursed

8	Imfinzi	Durvalumab L01XC28	Oncology	Reimbursed
9	Kymriah	Tisagenlecleucel	Oncology	Not reimbursed
10	Palynziq	Pegvaliase A16AB19	Phenylketonuria (PKU))	Not reimbursed
11	Onpattro	Patisiran N07XX12	Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)	Reimbursed
12	Adcetris	Brentuximab vedotin L01XC12	Oncology	Reimbursed
13	Kyprolis	Carfilzomib L01XX45	Oncology	Reimbursed
14	Darzalex	Daratumumab L01XC24	Oncology	Reimbursed
15	Sprycel	Dasatinib L01XE06	Oncology	Reimbursed
16	Xgeva	Denosumab M05BX04	Oncology	Reimbursed
17	Imbruvica	Ibrutinib L01XE27	Oncology	Reimbursed
18	Ninlaro	Ixazomib L01XX50	Oncology	Reimbursed
19	Tasigna	Nilotinib L01XE08	Oncology	Reimbursed
20	Iclusig	Ponatinib L01XE24	Oncology	Reimbursed
21	Cyramza	Ramucirumab	Oncology	Reimbursed
22	Actemra /RoActemra	Tocilizumab L04AC07	Oncology	Reimbursed

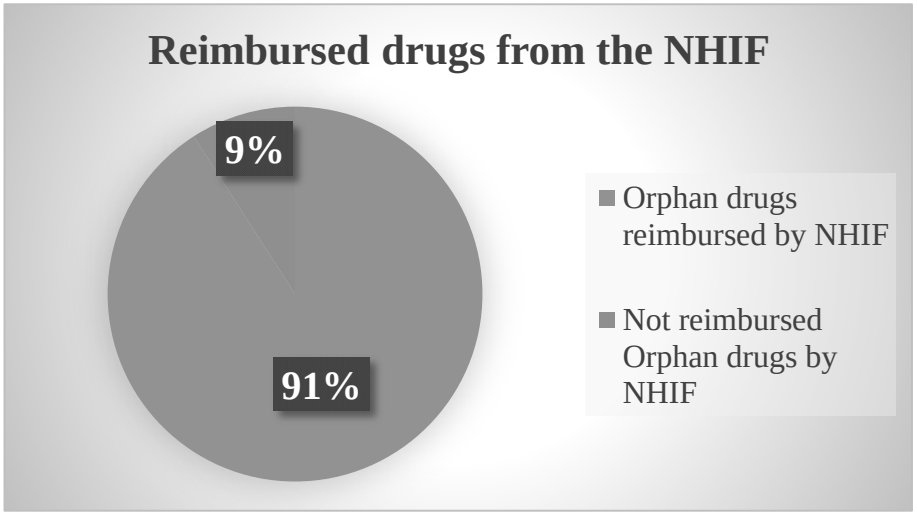

Figure 4. Reimbursed drugs from the NHIF

1. As a result of our own research, we identify that Lynparza is reimbursed targeted therapy by the NHIF and is an orphan drug used to treat ovarian cancer with BRCA mutation and fallopian tube cancer (European Medicines Agency, 2020; National Council On Prices and Reimbursement Of Medicinal Products, 2020). According to the results of the analyzed literature, the therapy is cost-effective treatment compared to platinum-based chemotherapy indicated for first-line treatment (Tan et al.,2019). In agreement with the health insurance fund in Italy, Lynparza as a maintenance

therapy could be cost-effective over a 50-year time horizon (Armeni et al.,2020; НАУКАOFFNEWS, 2018).

2. Vimizim is an orphan drug to treat a rare disease - Morquio syndrome, also known as Mucopolysaccharidosis Type IV (European Medicines Agency, 2020). The therapy is reimbursed by the NHIF and is cost-effective. According to the studied data, Vimizim proves its therapeutic efficacy and safety in clinical trials. Despite its high price of BGN 1,772.24 for a VAT wholesaler, Vimizim is an indispensable therapy for the treatment of this rare disease with proven health and economic benefits (National Council On Prices and Reimbursement Of Medicinal Products, 2020; Vekov & Tznakov,2018; Canadian Agency for Drugs and Technologies in Health (CADTH), 2015; Cooper et al.,2015).

3. Cerdelga is orphan drug reimbursed at the highest price by the NHIF and it has the price of a wholesaler with VAT - BGN 38,835.23, (National Council On Prices And Reimbursement Of Medicinal Products, 2020). The therapy is for the treatment of the rare Gaucher disease type 1 (European Medicines Agency, 2020; (Stoykova-Valcheva,2020). The results of our studies identify that the therapy could be cost-effective, but more research is needed to be done on the subject (Balwani et al., 2016; Smid & Hollak, 2014; National Institute For Health And Care Excellence,2016).

4. Blincyto is an orphan drug used to treat Acute lymphoblastic leukemia (ALL) for patients over 1 year of age (European Medicines Agency(2020). The National Health Insurance Fund (NHIF) reimburse the therapy and as a result of our studies, Blincyto is a cost-effective therapy compared to standard chemotherapy in the treatment of ALL. The orphan drug improves the life quality of patients (National Council On Prices And Reimbursement Of Medicinal Products,2020; Delea et al.,2017; Delea et al.,2019).

5. Alecensa is an orphan drug used to treat Non-small cell lung cancer (NSCLC) , тhe therapy is reimbursed by the NHIF. According to our studies, Alecensa is a cost-effective therapy compared to Xalkori, the Alecensa increases the chance of lack of disease progression (NSCLC) and improved quality of life (Carlson et al.,2018; Ravasio et al.,2019; Chu, 2017).

6. Bavencio is an orphan drug used as monotherapy in the treatment of adult patients with Merkel cell carcinoma, the therapy is reimbursed by the NHIF (European Medicines Agency, 2020; National Council On Prices And Reimbursement Of Medicinal Products,2020).The results of our studies are that Bavencio is not cost-effective compared to the other used therapy-Sutent (Bullement et al.,2019; Lu et al.,2020)

7. Rydapt is an orphan drug reimbursed by the NHIF. The therapy is cost effective in the treatment of newly diagnosed acute myeloid leukemia (AML) - a positive for FLT3 mutation (National Council On Prices And Reimbursement Of Medicinal Products, 2020; Stein et al.,2019; Tremblay et al., 2018).

8. Imfinzi is an orphan drug to treat locally advanced, inoperable non-small cell lung cancer (NSCLC). Targeted therapy is reimbursed by the NHIF.As a result of our research, Imfinzi is one of many examples where expensive immunotherapies are cost-effective and improve quality of life (European Medicines Agency, 2020; Criss et al.,2019, Armeni et al. 2020).

9. Kymriah is an orphan drug (European Medicines Agency, 2020) and as a result of our research this is the targeted therapy with the highest price that is allowed for use with the price of a wholesaler with VAT - 65 7170.88 BGN in Bulgaria, (NATIONAL COUNCIL ON PRICES AND REIMBURSEMENT OF MEDICINAL PRODUCTS,2020). The orphan drug is for the treatment of acute lymphoblastic leukemia (ALL) and Diffuse B-cell lymphoma (DLBCL) (European Medicines Agency, 2020; (Stoykova-Valcheva,2020). The results of our examination is that Kymriah is a cost-effective targeted therapy that contributes with over 9 years of life (Whittington et al.,2018;Slater,2020).

10. Palynziq is an orphan drug used to treat the rare genetic disease phenylketonuria (PKU). The therapy is approved for use in Bulgaria, but is not reimbursed by NHIF (European Medicines Agency, 2020, National Council On Prices And Reimbursement Of Medicinal Products,2020). The

results of the studies are that there is still no cost-effectiveness analysis for Palynziq, the treatment with the therapy could be cost - effective, if it increases life expectancy (Zori et al.,2019; Hydery & Coppenrath , 2019).

11. Onpattro is an orphan drug used to treat f hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) (European Medicines Agency,2020). Therapy for this rare disease is reimbursed by the NHIF. As a result of our research, Onpattro is a cost-effective therapy due to its high cost compared to the other best maintenance therapy. (Pharmacoeconomic Review Report, 2019; The Institute for Clinical and Economic Review (ICER) ,2018; Mickle et al., 2019).

12. Adcetris is an orphan drug for the treatment of Hodgkin's Lymphoma (European Medicines Agency, 2020). Targeted therapy is reimbursed by the NHIF and as a result of our studies, it is cost-effective, even in stage III / IV of the disease. (National Council On Prices And Reimbursement Of Medicinal Products, 2020; Caffrey,2018; Delea et al.,2019).

13. Kyprolis is an orphan drug used to treat multiple myeloma (European Medicines Agency, 2020). NHIF reimburse the therapy and, according to the studied literature, is cost-effective compared to Velcade (Amgen, 2012, Jakubowiak et al., 2016).

14. Darzalex is an orphan drug for the treatment of multiple myeloma (European Medicines Agency, 2020). NHIF reimburse the target therapy, as a result of our research, Darzalex is a cost-ineffective therapy due to its high cost (Zlang et al.,2018; Peligra et al.,2017).

15. Sprycel is an orphan drug for the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) (European Medicines Agency, 2020). NHIF reimburse the target therapy. As a result of our studies, Sprycel is a cost-effective targeted therapy compared to failed treatment with another therapy, Imatinib, due to patients' resistance to treatment (Taylor et al., 2012; Stoykova-Valcheva,2020).

16. Xgeva, an orphan drug (European Medicines Agency, 2020), reimbursed by the NHIF. As a result of our studies, this therapy is cost-effective in the treatment of advanced malignancies affecting the bones and contributes 7 years of life and QALYs 3.67., And leads to a long-term reduction in total costs (Terpos et al., 2019, Rasulova, 2013; Stoykova-Valcheva,2020).

17. Imbruvica is an orphan drug used to treat mantle cell lymphoma (European Medicines Agency, 2020). According to the literature, Imbruvica is a cost-ineffective therapy due to its high cost (Barnes, 2018, Patel et al., 2020).

18. Ninlaro is an orphan drug for the treatment of adult patients with multiple myeloma in combination with lenalidomide and dexamethasone (European Medicines Agency, 2020). NHIF reimburse the therapy and according to the results obtained, treatment with Ninlaro in combination with lenalidomide and dexamethasone is cost-effective compared to other alternative therapies, contributing to a better quality of life (Cai et al.,2019; Alkhatib et al.,2017).

19. Tasigna is an orphan drug (European Medicines Agency, 2020), for the treatment of chronic myeloid leukemia (CML). The therapy is reimbursed by the NHIF and the result of our research is that the orphan drug is a cost-effective, contributing to an additional 15 years saved life without disease progression (Romero et al.2014, Kantarjian et al., 2011; Stoykova-Valcheva,2020).

20. Iclusig is an orphan drug for the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia, the therapy is reimbursed by the NHIF. As a result of our research, targeted therapy is cost-effective, improving the health and quality of life of patients (Vellopoulou et al, 2017; The National Institute for Health and Care Excellence(NICE), 2017).

21.Cyramza is an orphan drug used to treat several diseases of stomach cancer, colorectal cancer, non-small cell lung cancer and hepatocellular carcinoma (European Medicines Agency, 2020). Targeted therapy is reimbursed by the NHIF. As a result of our research, Cyramza is a cost-effective therapy due to its minimal additional benefit and high additional costs for QALY (Saito et al.,2017; Zheng et al.,2020).

22. Actemra / RoActemra is an orphan drug for the treatment of rheumatoid arthritis (RA), the therapy is reimbursed by the NHIF (European Medicines Agency, 2020). As a result of the literature studied, treatment with Actemra / RoActemra is cost-effective for patients with

rheumatoid arthritis in need of biological monotherapy (Athanasakis et al.,2016;Diamantopoulos et al.,2012).

As a result of the studied cost-effectiveness analyzes of orphan drugs in Bulgaria, 15 orphan drugs are cost-effective, 2- orphan drugs could be cost-effective under certain conditions and 5- orphan drugs are cost-ineffective. (Figure 5)

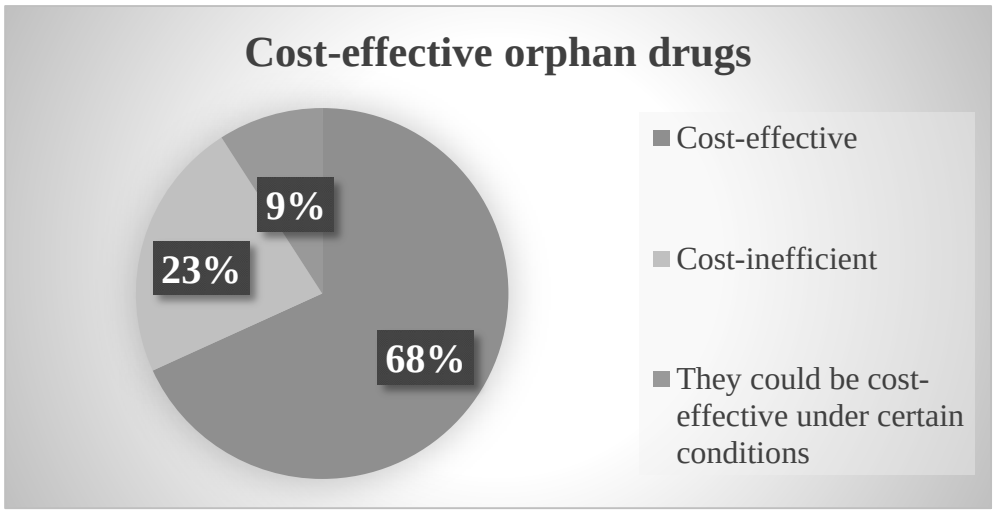

Figure 5. Cost-effective orphan drugs

Conclusion

In conclusion of our primary research the Bulgarian healthcare system faces the challenge of identifying the cost-effectiveness of expensive orphan drugs. The analysis of our research shows that despite of the high cost of orphan drugs, they are cost –effective with 68%, and they improve patients' quality of life. Many years the term rare disease indicate illness that affects very small percentage of the population, but nowadays in 2020, we could say that the rare disease are not so rare with count 300 million of people in 2020. In this scenario the healthcare systems and the patients have the need of cost-effective treatments - today presented by personalized medicine and orphan drugs.

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