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- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ПРОВЕДЕНИЯ ОЦЕНКИ ДОСТОВЕРНОСТИ НАУЧНЫХ ДАННЫХ С ПОМОЩЬЮ СИСТЕМЫ КЛАССИФИКАЦИИ, ОЦЕНКИ, РАЗРАБОТКИ И ЭКСПЕРТИЗЫ РЕКОМЕНДАЦИЙ GRADE
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

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PHARMACOECONOMIC ANALYSIS OF MEDICINES USED IN THE TREATMENT OF PULMONARY HYPERTENSION IN THE RUSSIAN FEDERATION

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Summary: *This article provides a comparative pharmacoeconomic evaluation of ambrisentan and bosentan used in the treatment of patients with functional class II or III pulmonary arterial hypertension (PAH) in Russia. The evaluation included methods of cost analysis, cost -minimization analysis, cost-utility analysis and budget impact analysis. The cost analysis revealed that the Volibris (ambrisentan) and Tracleer (bosentan) – associated costs, based on the per-patient per year treatment cost for one patient with PAH regardless of its functional class, were 1 585 649 rubles and 2 488 878 rubles, respectively. The results of cost-minimization analysis, based on the assumption of equal effectiveness of compared drugs, have shown that the per-patient per year treatment costs for Volibris (ambrisentan) allow cost savings of 909 789 rubles as compared to Tracleer (bosentan). The values of a cost-utility analysis for Volibris (ambrisentan) appeared to be lower than those for Tracleer (bosentan). For the former, depending on the functional class of the disease and drug dosage, the values of a cost-utility analysis varied from 2 321 771 rubles to 3 535 685 rubles per QALY, whereas for Tracleer (bosentan) the corresponding values were 4 335 477 rubles and 5 718 143 rubles per QALY in patients with functional class II PAH and functional class III PAH, respectively. The budget impact analysis, based on the estimated number of patients with PAH in RF of 3292 subjects, has shown that the total annual costs for Tracleer (bosentan) would be 8,193 billion rubles versus 5,219 billion rubles had the same patients been treated with Volibris (ambrisentan). Therefore, the possible cost savings with Volibris (ambrisentan) would be 2,973 billion rubles had it been used instead of Tracleer (bosentan), thus indicating that from the pharmacoeconomic perspective treatment with Volibris (ambrisentan) is a dominant choice.*

Key words: *pulmonary arterial hypertension, functional class, endothelin receptor antagonists, ambrisentan, bosentan, cost-minimization analysis, cost-utility analysis, budget impact analysis, decision tree.*

Introduction

Pulmonary arterial hypertension refers to a group of diseases characterized by progressive elevation in the pulmonary vascular resistance and pulmonary arterial pressure leading to right ventricular failure and premature death [1, 2]. According to patient survival data from the *Primary Pulmonary Arterial Hypertension (PAH)* Patient *Registry, 1981-1988, the death rate among patients with PAH was* 32% in the first year and 64% in the fifth year; and the estimated median survival time for these patients was 2.8 years [3]. The results of another US study based on the analysis of inpatient data also indicated the increased mortality rate (per 100 000 population) among patients with PAH during the 1999-2008 period [4] (Fig. 1). According to data from different registries, the aggregate prevalence of different types of PAH vary from 6.6 to 15 cases per one million population, and the morbidity rate for PAH is between 1.1 and 2.4 cases per one million population [5].

For characterization of PAH severity the WHO functional classification is used, that is a modified version of the New York Heart Association (NYHA) classification system developed for patients with circulatory insufficiency.

Class I – Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.

Class II – Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III – Patients with PAH resulting in marked limitation of physical activity. Less-than-ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

Class IV – Patients with PAH with inability to carry out any physical activity without symptoms. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity [2].

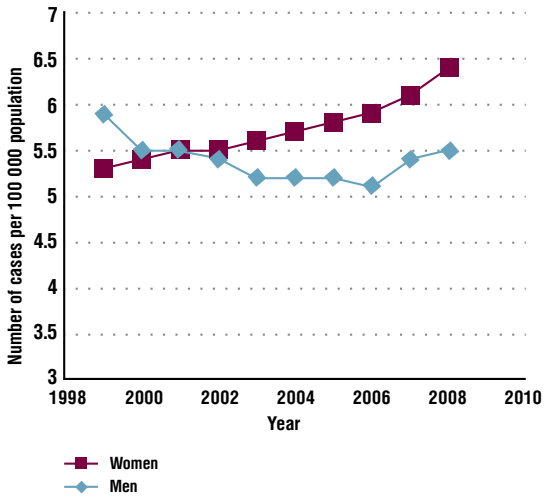

Figure 1. Age-standardized death rate for PAH per 100 000 population for men and women over the 1998 – 2010 period.

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There are different approaches to treatment of PAH including pharmacotherapy which consists of several drug classes [2]:

- Maintenance pharmacotherapy:
  - Anticoagulants;
  - Antiaggregants;
  - Diuretics;
  - Cardiac glycosides and inotropic agents.
- Specific pharmacotherapy:
  - Calcium channel blockers;
  - Prostaglandins;
  - Nitric oxide and phosphodiesterase type 5inhibitors;
  - Endothelin receptor antagonists.

The development of pharmacotherapy for PAH and expansion of the anti-PAH armory resulted in a significant increase in survival rate among patients with PAH. Compared to the above 1981-1988 data on PAH-related mortality, nowadays it has dropped to 9% in the first year and 43% over a 5-year period [5].

The endothelin receptor antagonists represent one of the most effective groups of pharmaceutical drugs (PD) used in the treatment of pulmonary arterial hypertension. Bosentan is the first PD from this group that was registered for the treatment of PAH in RF. To date, ambrisentan, another PD of this class, has been registered in Russia. According to results of randomized, double-blind, placebo-controlled, multicenter clinical trials conducted to evaluate the effect of ambrisentan in patients with PAH, 248 patients who completed a 48-week study protocol demonstrated a statistically significant improvement in parameters characterizing the disease [6]. Specifically, patients receiving ambrisentan had significantly increased their 6-minute walk distance, prolonged time to clinical worsening, improvement in WHO functional classification. Borg dyspnea score and quality of life measured by the SF-36 health survey [6]. A favorable safety profile of ambrisentan, the endothelin-1 receptor antagonist, is equally important for patients with PAH. In the course of clinical trials none of patients demonstrated more than a 3-fold increase in serum aminotransferase level against the baseline value. Moreover, ambrisentan therapy was not accompanied by an elevation of mean values of serum alanine aminotransferase, aspartate aminotransferase, total bilirubin and alkaline phosphatase compared to corresponding baseline values [6]. Therefore, ambrisentan enables to improve patients' functional status and their quality of life, and is well tolerated at that. This expands the possibilities of using ambrisentan in patients with PAH, e.g., in patients who develop hepatotoxicity while receiving bosentan [7]. However, the availability of PD for patients within the pharmaceutical benefits scheme implies that a given PD is included in a State-Sponsored Prescription Drug List. The procedure of drug inclusion in a State-Sponsored Prescription Drug List is specified in the RF Government Decree №871 of 28 August 2014 [8]. The pharmacoeconomic (clinicoeconomic) evaluation of PD is among the requirements which should be met in the proposal for the inclusion of PD in a State-Sponsored Prescription Drug List, in accordance with the RF Government Decree №871 of 28 August 2014 [8]. In this connection we deemed it appropriate to carry out a pharmacoeconomic study of ambrisentan (Volibris, GlaxoSmithKline) use in the treatment of patients with pulmonary arterial hypertension in Russian Federation.

As bosentan (Tracleer, Actelion Pharmaceuticals, Ltd.), the drug belonging to the same class as ambrisentan, is already included in the Vital and Essential Drugs List, we used it as a comparator in our pharmacoeconomic study. The study population was composed of patients with functional class II or III pulmonary arterial hypertension.

Therefore, the study aimed at pharmacoeconomic evaluation of ambrisentan in the treatment of patients with PAH. Our hypothesis was as follows: from the pharmacoeconomic perspective, ambrisentan is superior to bosentan in the treatment of patients with functional class II or III PAH.

Materials and Methods

This pharmacoeconomic study had a retrospective design and was carried out using the following methods of pharmacoeconomic analysis: effectiveness analysis, cost analysis, cost-minimization analysis (CMA), cost-utility analysis (CUA), budget impact analysis (BIA) and modeling [9, 11-15]. A decision tree type of modeling was used in this pharmacoeconomic analysis. The time horizon for the model was 1 year that normally spans the budget planning cycle in the healthcare system. The structure of the model is presented in Figure 2. This pharmacoeconomic study made use of data from the earlier conducted clinical trials and pharmacoeconomic studies, clinical manuals, patient information leaflets, online procurement portal, register of limitations on drug prices and price lists of medical institutions.

Results of pharmacoeconomic study of the use of Volibris (ambrisentan) in the treatment of pulmonary arterial hypertension

At the first step of this pharmacoeconomic study we performed the retrospective analysis of drug effectiveness by browsing on databases PubMed, Embase and Cochrane using "bosentan", "ambrisentan", "pulmonary arterial hypertension" as principal key words, and "pharmacoeconomic", "cost-effective", "QALY", "6MWD", "WHO FC", "Borg Score" as additional key words. The results of systematic review encompassing over 100 publications failed to reveal any clinical data attesting to statistically significant differences in effectiveness between the two compared drugs. Moreover, we found several studies which did not find any significant differences between ambrisentan and bosentan. Thus, for example, Dranitsaris G. et al. 2009 [16] carried out an indirect comparison of clinical trials that used either ambrisentan or bosentan and concluded that there were no significant clinical differences between the two. Guillermo Villa et al. 2013 [17] in a pharmacoeconomic study also found no significant differences between ambrisentan and bosentan. Our literature search found a study by Meghan Aversa et al. 2015 [18] which demonstrated a better safety profile for ambrisentan. Specifically, it was found that bosentan more often than ambrisentan caused hepatotoxicity which resulted in drug withdrawal. Considering different frequency of adverse effects with each drug, Kathryn Coyle et al. 2016 [19] calculated QALY[1] values for ambrisentan and bosentan using a Markov model. For a patient with functional class II and

[1] QALY (Quality-adjusted life year) is a year of perfect health. This parameter is considered in pharmacoeconomics as the most convincing criterion of effectiveness from the decision-making perspective. QALY is determined as life expectancy multiplied by health-related quality of life. One QALY equates to one year in perfect health.

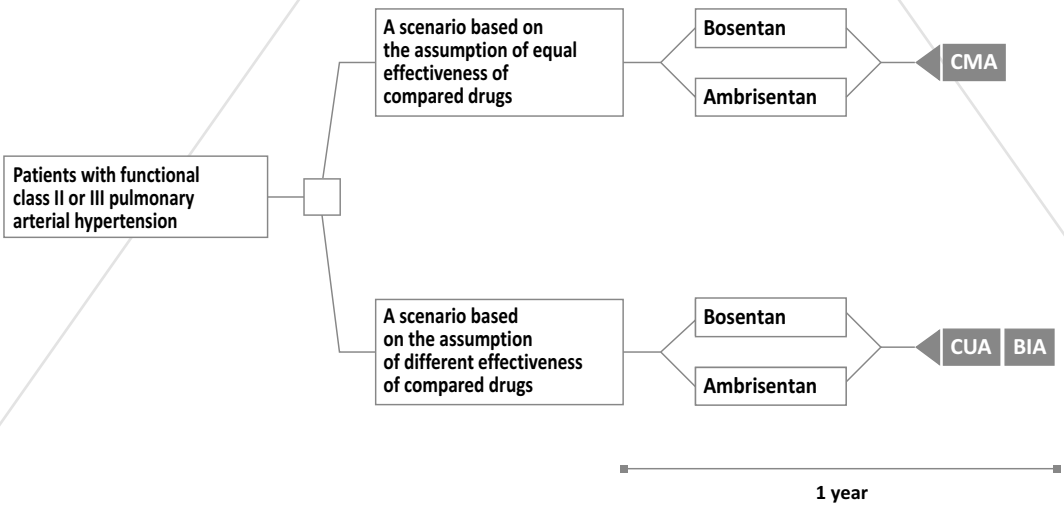

Figure 2. Structure of the decision tree model.

functional class III pulmonary arterial hypertension and a life expectancy of 30 years, treatment with ambrisentan 5 mg or 10 mg provides 4.634 (4.217) QALY and 3.180 (3.043) QALY, respectively, while for bosentan the respective values were 3.904 QALY and 2.960 QALY.

Considering that our literature search brought up papers with disagreeable conclusions, we decided to employ two scenarios in our pharmacoeconomic study. The first one was based on the assumption that the compared drugs are equally effective and, hence, implied the use of the cost-minimization method. The second scenario was based on the results of Kathryn Coyle et al. 2016 [19] whose conclusions were indicative of significant differences in QALY between ambrisentan and bosentan owing to different safety profiles of the two drugs. According to the methodology of pharmacoeconomic analysis, in the second scenario we should use the cost-utility analysis. At the same time, the Markov model employed in the paper by Kathryn Coyle et al., 2016 had a time horizon of 30 years (i.e., patients' life expectancy), at a discount rate of 5%. For this reason, and given the one-year time horizon in the above study, their QALY values were adjusted to meet the requirements of our study assuming that QALYs accumulate linearly with duration. At the first step of adjustment we calculated the undiscounted QALYs for each drug using the following equation [9]:

ResultND = ResultD/(1-(0,05))^(30-1) Equation (1)

where:

ResultD – discounted result;
ResultND – undiscounted result;
0.05 – discounting coefficient;
30 – time horizon, years.

The obtained QALY values are presented in Table 1.

Table 1. Results of effectiveness analysis

INN	Dosage, mg	Functional class of the disease	QALY gain per-patient per year
Ambrisentan	5	II	0.6834
Ambrisentan	10	II	0.6221
Ambrisentan	5	III	0.4692
Ambrisentan	10	III	0.4490
Bosentan	-	II	0.5760
Bosentan	-	III	0.4367

Cost analysis results

In this study direct costs were taken into consideration. The direct costs were comprised of costs for basic pharmacotherapy for pulmonary arterial hypertension using endothelin receptor antagonists and medical services (including diagnostic procedures). Given that the studied drugs were prescribed in the outpatient setting, costs for basic pharmacotherapy were calculated based on the required number of drug packages per year. At the first step of cost analysis we calculated the annual cost of a course of therapy with studied drugs per one patient. When calculating costs for Tracleer (bosentan), we used the average auction price per package based on the results of tenders completed in 2016 [20]. The price was 177 777 rubles and was the same for both pharmaceutical form 65.5 mg N 56 and pharmaceutical form 125 mg N 56. Price for Volibris (ambrisentan) was obtained from a similar source and was 121 973 rubles for both pharmaceutical form 5 mg N30 and pharmaceutical form 10 mg N30. Therefore, giving the pricing policy conducted by distributors in RF, the costs of pharmacotherapy with Volibris (ambrisentan) and Tracleer (bosentan) appeared to be the same for both basic and high drug dosages. Given that the studied drugs were prescribed in the outpatient setting, the cost of a course therapy was calculated based on the number of packages.

The cost of a one-year course of therapy with Volibris (ambrisentan) was as follows (Fig.3):

Cost (Volibris 5 mg) = 121973*13 = 1585649 rub.
Cost (Volibris 10 mg) = 121973*13 = 1585649 rub.

The cost of a one-year course of therapy with Tracleer (bosentan) appeared to be higher (Fig.7):

Cost (Tracleer 65.5 mg) = 177777*14 = 2488878 rub.
Cost (Tracleer 125 mg) = 177777*14 = 2488878 rub.

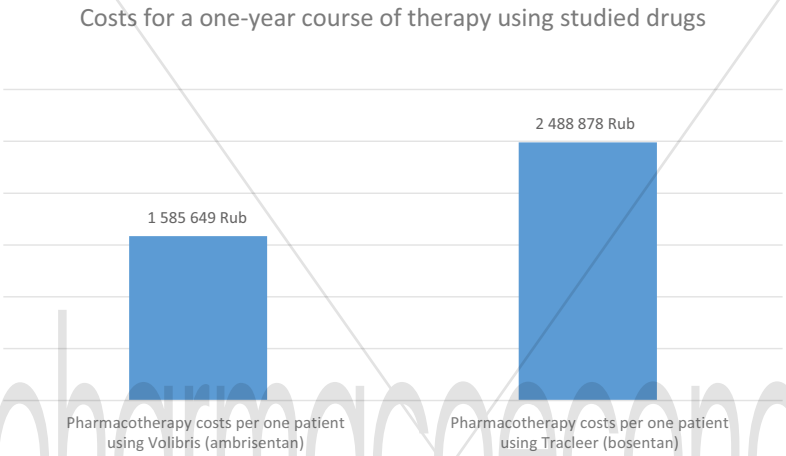

Figure 3. Results of basic pharmacotherapy cost analysis

At the next step of cost analysis we determined other drug-related direct costs, specifically, for laboratory tests for liver enzymes and hemoglobin levels. Costs of laboratory tests were derived from the price list of the InVitro company [21], according to which the cost of measurement of serum aspartate aminotransferase and alanine aminotransferase levels is 265 rubles, and that for serum hemoglobin level is 315 rubles. Considering the frequency of laboratory tests [2], the annual costs for those per patient for Volibris (ambrisentan) were:

CostS (Volibris) = 2*315+2*265+2*265 = 1690 rub.

Annual costs for laboratory tests per patient for Tracleer (bosentan), if used in accordance with its Patient Information Leaflet [14], were:

CostS (Tracleer) = 6*315+12*265+12*265 = 8250 rub.

Therefore, the total per patient per year costs for each drug regardless of drug dosage were 1 587 339 rub. for Volibris (ambrisentan) and 2 497 128 rub. for Tracleer (bosentan).

Results of cost-minimization analysis

The cost-minimization analysis was based on the results of cost analysis and an assumption that ambrisentan and bosentan have equal clinical effectiveness. In such case the cost-minimization analysis is defined as a difference in total costs for each drug per patient per year. According to data presented in Fig. 4, from the cost minimization perspective treatment with Volibris (ambrisentan) is the dominant choice as this allows cost savings of 909 789 rubles compared to treatment with Tracleer (bosentan).

Results of cost-utility analysis

The cost-utility analysis is performed to compare drugs with different efficacy which is expressed in the same units, the QALYs. The purpose of cost- utility analysis is to comparatively measure the cost/utility index for each studied drug, and the cost/utility index is calculated as the ratio of cost to QALY saved due to treatment with a given drug.

The results of the cost-utility analysis can be interpreted as follows. From

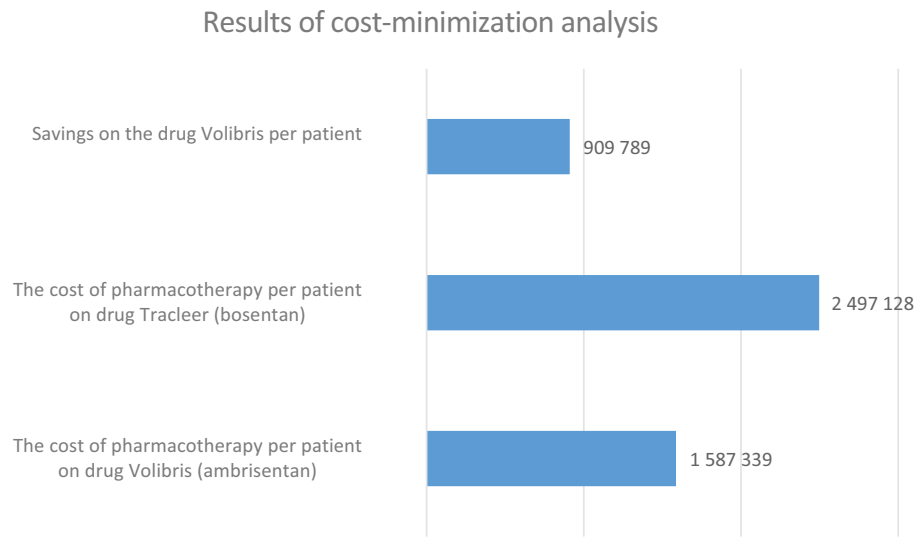

Figure 4. Results of cost-minimization analysis

the cost utility perspective a pharmaceutical drug can be recognized as:

- «strongly preferred» or dominant choice when it has a lower cost/utility index along with better therapeutic effectiveness;
- «cost-effective» when it demonstrates better therapeutic effectiveness along with higher cost/utility index which fits into the acceptable for a given healthcare system limits of preparedness to pay (characterized by an incremental cost-utility ratio not exceeding the limit of preparedness to pay);
- «non-efficacious» when a pharmaceutical drug has a higher cost/utility index along with lower therapeutic effectiveness, or when its incremental cost-utility ratio exceeds the acceptable for a given healthcare system limits of preparedness to pay [9,14].

Our cost-utility analysis is based on the effectiveness analysis (Table 1) and cost analysis (Fig. 7). The cost-utility ratio was calculated for studied drugs in patients with functional class II or III pulmonary arterial hypertension. In accordance with results of effectiveness analysis we evaluated separately cases when Volibris (ambrisentan) was used at a daily dose of 5 or 10 mg. The calculations of cost-utility ratios for the two drugs are given below.

CUR (Volibris 5 mg, functional class II) = (1585649+1690)/0.6834 = 2321771 rub./QALY

CUR (Volibris 10 mg, functional class II) = (1585649+1690)/0,6221 = 2551361 rub./QALY

CUR (Tracleer, functional class II) = (2488878+8250)/0.5760 = 4335477 rub./QALY

CUR (Volibris 5 mg, functional class III) =(1585649+1690)/0.4692 = 3383361 rub./QALY

CUR (Volibris 10 mg, functional class III) = (1585649+1690)/0.4490 = 3535685 rub./QALY

CUR (Tracleer, functional class III) = (2488878+8250)/0.4367 = 5718143 rub./QALY

As can be seen from data presented in Figure 5, Volibris (ambrisentan) is characterized by lower cost-utility ratio and, therefore, can be considered as a dominant alternative. The incremental cost-utility analysis is not required in this case.

Results of budget impact analysis

The budget impact analysis allows us to determine and identify necessary expenses toward treatment of patient population using any given pharmaceutical drug. In our study we compared annual budgets allocated to treatment of all Russian patients with pulmonary arterial hypertension for whom therapy with endothelin receptor antagonists is indicated, provided the prescribed drugs were Volibris (ambrisentan) or Tracleer (bosentan). Population of patients with pulmonary arterial hypertension in need for treatment with endothelin receptor antagonists was calculated as a result of multiplication of total RF population [10], prevalence of disease (45/1 000 000, the mean

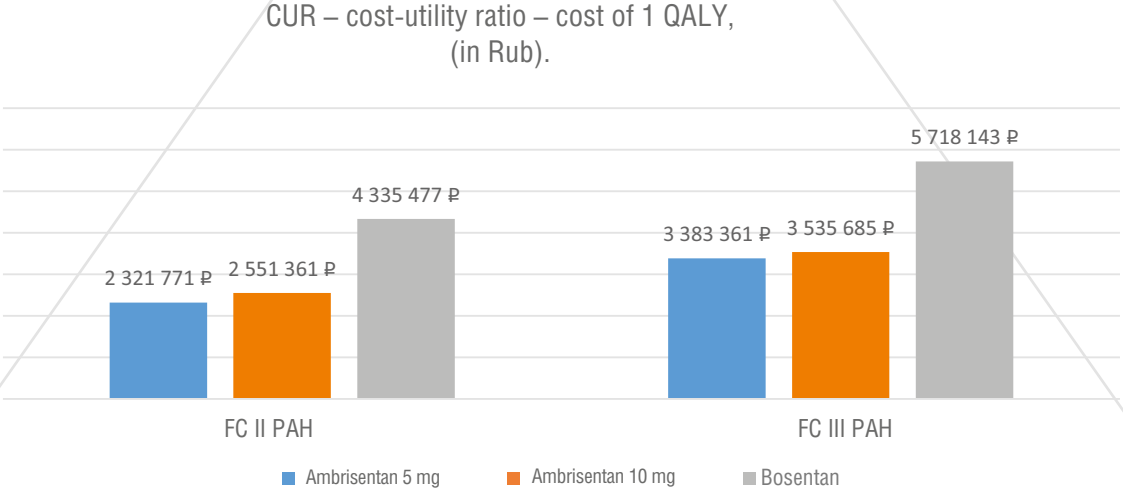

Figure 5. Results of cost-utility analysis

value within the range from 30 to 60 cases per 1 000 000 population) [2] and prescription frequency (0.5) of a given class of pharmaceutical drugs to patients according to standard of care [11]. Therefore, the number of patients was 3292. If we hypothetically propose to switch patients to Volibris (ambrisentan), the annual budget for treatment of patients with pulmonary arterial hypertension would be 5,219 billion rubles, while in a current situation when all patients are supposed to be treated with Tracleer (bosentan) such treatment costs are 8,193 billion rubles (Fig. 6). Hence, treatment of all patients with PAH using Volibris (ambrisentan) instead of Tracleer (bosentan) should yield savings in expenditure amounting to 2,973 billion rubles.

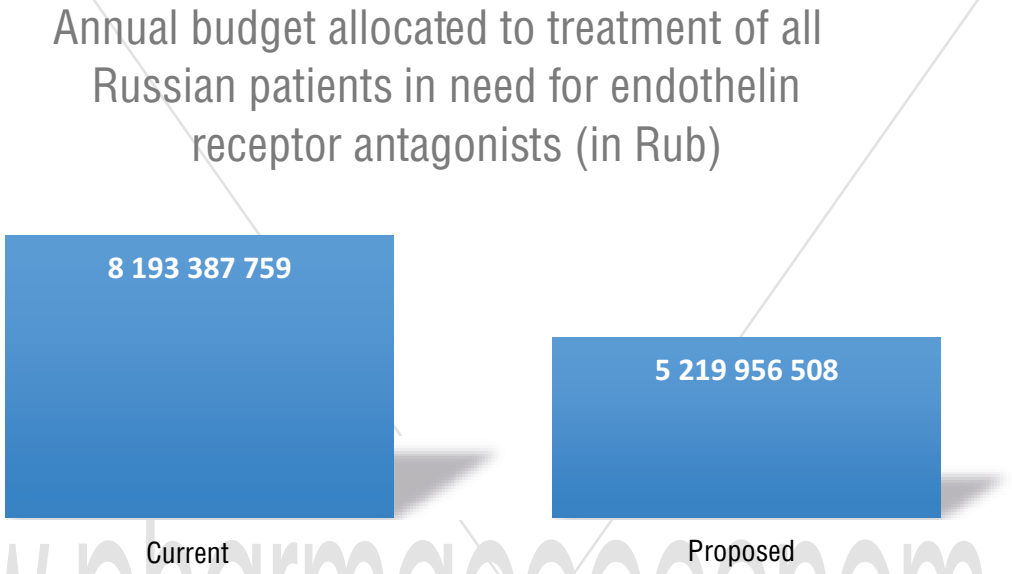

Figure 6. Results of budget impact analysis

Sensitivity analysis

Based on the results of pharmacoeconomic analysis attesting to superiority of Volibris (ambrisentan) over Tracleer (bosentan), we deemed it necessary to set the degree of stability for the conclusions obtained. In this connection we carried out a one-way (univariate) sensitivity analysis taking the cost of Volibris (ambrisentan) as the most significant factor. For the sensitivity analysis, the per package price of Volibris (ambrisentan) was increased by 30% to 158658 rubles. The per patient per year costs for Volibris (ambrisentan) rose to 2 061 344 rubles but still remained below those for Tracleer (bosentan). After a 30% price increase for Volibris (ambrisentan) the values of cost-utility ratio increased to 3017561 and 3315954 (4397289 and 4595261) for 5 mg and 10 mg dosages, respectively, used to treat functional class II and III PAH, but still remained below those for Tracleer (bosentan). From the cost minimization perspective, even after a 30% price increase Volibris (ambrisentan) still remained a less costly alternative that provided savings of 434 095 rubles per patient per year compared to Tracleer (bosentan). This allows us to acknowledge the stability of conclusions which we came to in this pharmacoeconomic study.

Conclusions

1. An interactive pharmacoeconomic model (the calculator) has been developed to evaluate treatment of patients with functional class II and III pulmonary arterial hypertension using ambrisentan and bosentan.
2. Our pharmacoeconomic analysis allowed us to calculate the per patient per year costs associated with use of Volibris (ambrisentan) and Tracleer (bosentan) in patients with pulmonary arterial hypertension, and, regardless of the functional class of the disease, these costs were 1 585 649 rubles and 2 488 878 rubles, respectively.
3. Results of the cost-minimization analysis have shown that Volibris (ambrisentan) provides cost savings of 909789 rubles per patient per year compared to Tracleer (bosentan).
4. The cost-utility ratio for Volibris (ambrisentan) appeared to be lower than that for Tracleer (bosentan). For the former, depending on the functional class of the disease and dosage, the costs varied from 2 321 771 rub. to 3 535 685 rub. per QALY, whereas for Tracleer (bosentan) the corresponding values were 4 335 477 rub. and 5 718 143 rub. per QALY for patients with functional class II and III PAH, respectively. Therefore, from the cost utility prospective, Volibris (ambrisentan) can be considered as a dominant choice.

The budget impact analysis, which was based on the assumption that the number of patients with PAH in RF is equal to 3292 subjects, has shown that their treatment with Tracleer (bosentan) for one year will need the expenditure amounting to 8,193 billion rubles whereas their treatment with Volibris (ambrisentan) will cost 5,219 billion rubles. Hence, treatment of all patients with PAH using Volibris (ambrisentan) instead of Tracleer (bosentan) should yield savings in expenditure amounting to 2,973 billion rubles.

A one-way (univariate) sensitivity analysis demonstrated stability of our pharmacoeconomic conclusions within Volibris cost variability ± 30%.

We confirmed the study hypothesis that ambrisentan is superior to bosentan in the treatment of patients with functional class II and III pulmonary arterial hypertension from the cost effectiveness perspective.

Conclusion

The results of our pharmacoeconomic evaluation has revealed superiority of Volibris (ambrisentan) over Tracleer (bosentan) in the treatment of patients with functional class II and III pulmonary arterial hypertension from the cost utility perspective. Volibris (ambrisentan) is characterized by lower cost-utility ratio. From the cost minimization and budget impact perspective, Volibris (ambrisentan) also represents a dominant alternative as it needs less federal spending and enables to save on healthcare costs as compared to Tracleer (bosentan).

In accordance with provisions of the Decree of RF Government of 28.08.2014 "On the approval of rules over formation of the check-list of medicinal drugs for medical use and the minimal range of pharmaceutical drugs required for provision of medical aid", on the clinicoeconomic (pharmacoeconomic) scale Volibris (ambrisentan) receives **+7 scores** as its use results in 36% reduction in pharmacotherapeutic costs (+2 scores) and total costs (+4 scores) as compared to Tracleer (bosentan), and has advantages judging by results of the cost-utility analysis (+1 score).

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