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PHARMACOECONOMIC ANALYSIS OF FOSTER® USE IN THE TREATMENT OF BRONCHIAL ASTHMA

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Abstract: *The correct treatment of bronchial asthma is a difficult task not only for patients and healthcare professionals but for healthcare authorities as well. The economic burden of the disease is equal to the burden of diabetes mellitus and arterial hypertension. Nearly all indirect costs and not less than a third of direct costs of the treatment of the disease are related to management of exacerbations and poor asthma control. In recent years, there has been a considerable improvement in the treatment of asthma associated with emergence of new medicinal products and delivery devices. Unfortunately, not every patient is able to achieve the optimal disease management level. For this reason, technologies for creation of an effective treatment method for bronchial asthma are undergoing continual improvement nowadays. One of the solutions in this field was the development of inhaler devices producing extrafine aerosol with particle diameter under 2 μm. Such aerosols make it possible for inhalation medicines to reach the small airways, which are the principal site of inflammation in a number of bronchial asthma phenotypes (including bronchial asthma in smokers). The objective of this study was to determine the advantageous medicinal product for bronchial asthma using pharmacoeconomic analysis, on the basis of comparison between costs and effectiveness, safety, and quality of life in treatment with fixed combinations of inhaled glucocorticosteroids and long-acting β_2-agonists: medicinal products (MP) Foster®, Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk. According to the results of the cost-utility analysis, it was determined that the therapy with Foster® is dominant and characterized by the lowest costs with reference to QALY compared to Symbicort® Turbuhaler® and is cost-effective compared to Seretide® and Seretide® Multidisk, on the basis of the obtained values of the incremental cost-utility analysis, which are significantly lower than the willingness-to-pay threshold in the Russian Federation. The budget impact analysis demonstrated that using Foster® for therapy results in budget savings compared to Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk when transferring an additional number of patients (21 %) to Foster®.*

Keywords: *Foster®, extrafine beclometasone, combination therapy, bronchial asthma, asthma control, inhalation route of delivery, cost analysis, cost-utility analysis, incremental cost-utility analysis, budget impact analysis, pharmacoeconomics.*

Introduction

Bronchial asthma (BA) is a chronic disease of the upper respiratory tract, which places a heavy social and economic burden on patients, their families, and society as a whole [1, 2, 4]. According to the statistical data of the Ministry of Healthcare (MH RF), the total number of BA patients in Russia is approximately 1.5 million [17]. The adult population constitutes 76% of them. Numerous therapeutic achievements and profound understanding of pathophysiology of the disease have made it possible to achieve a more efficient asthma control. However, despite these improvements, BA remains one of the ten chronic diseases, the treatment of which entails the highest costs. The impact of this disease is significant. An ineffective therapy of BA places major restrictions on professional activities and physical activity, causes premature mortality [2, 5], and is associated with the increase in economic expenses worldwide [7]. Medical costs related to rendering aid to bronchial asthma patients in Russia are RUB 8.5 billion per year. The major part of these expenses (66.6%) is inpatient care, i.e. therapy of exacerbations of the disease [26].

In spite of the fact that a large number of medicinal products have emerged on the pharmaceutical market in recent decades, BA prevalence is steadily increasing; its clinical presentation is changing as well: severe, difficult-to-treat forms are continuously on the rise, which is confirmed by the increasing number of hospitalizations and fatal outcomes, the reason for which is bronchial asthma. These peculiarities determine the high medical and social significance of this disease, prompting the search for new effective methods to achieve control over the disease progression [3]. One of the factors hindering BA control is persistent small airway (SA) inflammation. Affecting this component of pathogenesis can have a major clinical significance, especially in certain BA phenotypes (including bronchial asthma in smokers) [10, 19]. Metered-dose inhalers (MDI) are most commonly used in the treatment of BA [2, 7, 9]. A product dose released by an MDI is easily reproducible. However, many inhalers of this type have a major shortcoming that is a large size of particles released, resulting in poorer asthma control as a consequence of incomplete delivery of medicinal substances to SA as well. One of the solutions in this field was the development of inhaler devices that make it possible for medicines to reach SA by producing extrafine aerosol (aerosol with the average aerodynamic particle diameter under 2 μm). There is currently only one extrafine fixed combination of an inhaled glucocorticosteroid (IGCS) and a long-acting β2-agonist (LABA): beclometasone dipropionate/formoterol (BDP/FOR, Foster®) delivered via Modulit system. The average aerodynamic particle diameter of IGCS and LABA in the fixed combination BDP/FOR is about 1.5 μm, which enables their even distribution in both proximal and distal airways, exerting anti-inflammatory and broncholytic action throughout the whole bronchial tree [10]. This particle size is mostly achieved due to the special valve design of the delivery device and the change of geometrical shape of its holes: in addition, these characteristics of the Modulit MDI enable to reduce the velocity of the aerosol jet, thereby solving another problem (that is common to patients with bronchial asthma) of complicated coordination of inhaler activation and performing inhalation of the drug [29]. All this, in its turn, manifests itself as higher clinical effectiveness compared to conventional, non-extrafine BDP and formoterol products delivered from separate inhalers [10].

High social and economic significance of BA, availability of a wide range of medicinal products (MP), and limited financial resources of the healthcare system are the basis for the pharmacoeconomic (PEC) analysis of different types of treatment for bronchial asthma.

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The objective of this study was to determine the advantageous medicinal product for bronchial asthma using pharmacoeconomic analysis, on the basis of comparison between costs and effectiveness, safety, and quality of life in treatment with fixed combinations of IGCS and LABA: Foster®, Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk.

The following tasks were sequentially carried out to achieve the set objective:

1. Identification of modern approaches to the treatment of bronchial asthma patients
2. Information search for results of randomized clinical trials of effectiveness of modern treatment methods for this nosology
3. Information search for complete pharmacoeconomic studies of medicinal products used for treatment of this nosology
4. Calculation of BA therapy cost for the following medicinal products (MP): Foster®, Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk
5. Cost analysis, cost-utility analysis, and budget impact analysis for the medicinal products under comparison.

Comparison options and data sources

In accordance with the objective and tasks set, the first stage of the study included the information search for available publications in PubMed, Medlink, and Cochrane databases. The choice of treatment regimens for bronchial asthma patients was based on the data from Russian and international recommendations [1, 3, 6, 8], according to which the priority line in the therapy of moderate-to-severe bronchial asthma is combinations of inhaled glucocorticosteroids and long-acting β2-agonists. This study considered their fixed combinations: beclometasone/formoterol, budesonide/formoterol (BUD/FOR), salmeterol/fluticasone (SAL/FL). MP Foradil Combi was excluded from the PEC analysis because it is a free combination of budesonide and formoterol in one device but different capsules, and the substances are released sequentially. Therefore, the search query included the following keywords: “asthma”, “clinical trial”, “asthma control”, “combination therapy”, “extrafine beclometasone/formoterol”, “fixed combination”, “moderate-to-severe asthma”, and “inhaler”. In addition, the search was done in the database “Russian Medicine” of the Central Scientific Medical Library of I.M. Sechenov First MSMU, the scientific electronic library elibrary.ru, and free search engines such as Yandex, Google, etc. The information search included the following keywords: “bronchial asthma”, “asthma control”, “extrafine aerosol”, “combinations of inhaled glucocorticosteroids and long-acting β2-agonists”, “effectiveness”, “clinical trial”, “fixed combinations”, “beclometasone/formoterol”, “Foster®”, “salmeterol/fluticasone”, “budesonide/formoterol”, “vilanterol/fluticasone”, “moderate asthma”, and “severe asthma”. This search query yielded several thousands of publications. Then, duplicate publications and trials unrelated to BA treatment were excluded. In addition, the further analysis did not include randomized clinical trials (RCT) where medicinal products under comparison were compared only to placebo but not to each other, publications of preliminary results, and articles in foreign languages other than English. To be included into the analysis, trials should have contained the information about the number of exacerbations, changes in pulmonary function, mortality, frequency of adverse reactions, and quality of life under the section “Results”. The level of evidence was determined in accordance with the grading scales of level of evidence for results of clinical trials (CT) of medicinal products and strength of evidence for clinical trials of medicinal products. Preference was given to trials with level of evidence A or B: evidence summarized in a systematic review, in a meta-analysis, and evidence obtained in prospective RCT, respectively. Then, 32 results with CT were obtained (there were no meta-analyses among them), which were subjected to additional evaluation. The main selection criterion at this stage was the presence of direct and simultaneous comparison of all combination products in IGCS/LABA group. No direct comparative trials of the MP Relvar Ellipta® versus all alternative MP at the same time were found during the information search; therefore, the product was not included into further PEC analysis. As a result, three publications that met this criterion were selected: Müller et al., Allegra et al., and Terzano et al. [27, 21, 22]. The trials compared three combinations against each other: BDP/FOR, BUD/FOR, and SAL/FL. At the same time, two publications were parts of one prospective trial of asthma control (PRISMA): long-term [22], lasting for one year, and short-term [21]. Following comparison of the trials, PRISMA was chosen for analysis; its advantages are given in the Table 1.

Table 1. Brief comparison of the trials:

Müller et al. [27]	PRISMA (Allegra et al. [21] and Terzano et al. [22])
• Small number of patients in the trial (n=111) • No individual data for each of the fixed combinations (data for BUD/FOR and SAL/FL are combined) • The author’s questionnaire using GINA criteria is used for evaluation of BA control level	• Large number of patients in the trial (n=2,853) • Data for each of the three fixed combinations • EQ-5D quality of life questionnaire was used for evaluation of the results • The frequency of exacerbations is given • Incidence of emergency aid and outpatient and inpatient care is given only for the short-term part of the trial

Thus, pharmacoeconomic evaluation of Foster® used as monotherapy for bronchial asthma versus Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk was conducted on the basis of the data obtained from the information search. The analysis excluded the following MP: Foradil Combi® and Relvar Ellipta®, as they did not meet the initial criteria of the analysis and were lacking the necessary data in the results of the information search, respectively.

Effectiveness analysis

In accordance with the guidelines of the Global Strategy for Asthma Management and Prevention (GINA) on BA control and the information search performed, effectiveness criteria were determined, which made it possible to conduct pharmacoeconomic evaluation of stated pharmacotherapy options: QALY value [12], according to PRISMA trial [21, 22]. Also, the effectiveness at this stage was evaluated on the basis of comparison of exacerbation frequency [21, 22]. The data obtained are given in Table 2.

Table 2. Results of the effectiveness analysis

Trade name	QALY 1 year	Frequency of exacerbations
Foster®	0.89	13.30%
Symbicort® Turbuhaler®	0.82	13.10%
Seretide®	0.87	20.30%
Seretide® Multidisk	0.87	20.30%

On the basis of the effectiveness analysis performed, it can be concluded that the use of Foster® for treatment of BA patients makes it possible to achieve a higher quality of life value compared to other combinations of IGCS/LABA and is associated with a lower incidence of exacerbations compared to Seretide® and Seretide® Multidisk, which results in a better asthma control.

Cost analysis

The next stage of the study evaluated the costs of monotherapy, outpatient care, and management of adverse reactions and exacerbations.

Considering the data from randomized clinical trials [21, 22] and recommendations given in instructions for use [20, 23-25], the 365-day time horizon of the options under comparison was analyzed, and daily doses of the fixed combinations were determined. Monotherapy costs were calculated using prices from the Vital and Essential Drugs List for March 2017 [18], considering the time horizon and the daily dose of MP (Table 3).

Table 3. MP cost and dosage regimen

Presentation		Dosage regimen		Package price, RUB	Daily dose price, RUB
number of doses, units	1 dose, μg	Required number of doses	Number of days		
Foster® (inhalation aerosol)					
120	100+6	4	365	1 900	63
Symbicort® Turbuhaler® (inhalation powder)					
60	320+9	2	365	2 182	73
60	80+4,5	4	365	900	60
120	80+4,5	4	365	1 678	56
60	160+4,5	4	365	1 177	78

Presentation		Dosage regimen		Package price, RUB	Daily dose price, RUB
number of doses, units	1 dose, μg	Required number of doses	Number of days		
120	160+4,5	4	365	2 198	73
Seretide® (inhalation aerosol)					
120	25+50	4	365	864	29
120	25+125	4	365	1 126	38
120	25+250	4	365	1 718	57
Seretide® Multidisk (inhalation powder)					
60	50+100	2	365	914	30
60	50+250	2	365	1 205	40
60	50+500	2	365	1 611	54

At the time of the pharmacoeconomic study, the Order of the Ministry of Healthcare and Social Development of the Russian Federation No. 600 as of September 17, 2007, "On Adoption of the Standard of Care for Asthma Patients" (hereinafter the "Standard") was in effect in the Russian Federation [15]. According to the regulatory document, the calculation of cost of outpatient and polyclinic care uses the data from the list of services for BA diagnosis and treatment, excluding pharmacotherapy in the outpatient setting. The cost of services was determined on the basis of medical aid rates of the Compulsory Medical Insurance Fund (CMIF) of Moscow for 2016. Thus, the cost of outpatient care for BA patients in remission was RUB 1,534 and in exacerbation – RUB 4,810.

Then, the cost of management of exacerbations and treatment of adverse reactions was calculated. Owing to the lack of data in the longitudinal phase of PRISMA trial [22] about the type of exacerbation outcome, it was assumed in calculation of exacerbation management costs that each case of exacerbation reported in the trial ended in hospitalization. The data on the cost of hospitalization were taken from the rates of the Compulsory Medical Insurance Fund of Moscow and constituted:

1. Mild-to-moderate asthma in adults: RUB 24,449. Hospitalization period: 18 days.
2. Severe asthma in adults: RUB 32,473. Hospitalization period: 21 days.

When calculating the costs of adverse reaction management, type and frequency of adverse reactions were determined according to instructions for medical use of the MP under comparison [20, 23 – 25], owing to the lack of these data in CT. Adverse reactions were grouped by frequency of occurrence as follows: very common (>1/10); commono (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), isolated reports (frequency cannot be estimated). The cost of management of adverse reactions was calculated considering the frequency stated above and using the currently effective Standards of Care and rates of CMIF of Moscow.

Thus, the estimates of the total cost of therapy in the treatment groups under comparison were calculated on the basis of the cost of diagnosis and treatment with primary pharmacotherapy and management of exacerbations and adverse reactions and the data on duration of treatment of BA patients (Table 4).

Table 4. Results of cost analysis per patient for 1 year

Trade name	Foster®	Symbicort® Turbuhaler®	Seretide®	Seretide® Multidisk
Pharmacotherapy, RUB	24,700	26,136	16,064	16,166
Outpatient care, RUB	1,534	1,534	1,534	1,534
Management of exacerbations, RUB	3,252	3,203	4,963	4,963
Management of adverse reactions, RUB	571	652	1,032	1,024
Total costs, RUB	30,056	31,524	23,594	23,686

On the basis of the results obtained, it can be concluded that the use of Foster® for BA treatment is more economically advantageous compared to Symbicort® Turbuhaler®.

Cost-utility analysis

The cost-effectiveness analysis with reference to treatment of one BA patient was performed in the course of the pharmacoeconomic study. As the time horizon did not exceed one year, costs were not discounted. The cost-utility ratio, obtained in the treatment groups of Foster®, Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk was calculated using the formula [13, 16]:

$$CUR = \frac{DC}{Ut}, \quad (1)$$

where: CUR is the cost-utility ratio;

DC is the cost of medical technology, RUB;

Ut is the medical technology effectiveness value.

The following results of the cost-utility analysis were obtained for the options under comparison in BA therapy with reference to one patient and utilizing the QALY value as the effectiveness criterion (Figure 1).

On the basis of the results of the cost-effectiveness analysis, it can be concluded that the use of Foster® for BA treatment is characterized by the lowest costs for the unit of effectiveness considered compared to Symbicort® Turbuhaler®. This indicates achieving a better BA control and, accordingly, a higher effectiveness of the product with less economic costs.

Incremental cost-utility analysis

Owing to the fact that the therapy with Foster® is characterized by both the highest costs and the highest effectiveness expressed in QALY compared to Seretide® and Seretide® Multidisk, the incremental cost-utility ratio was calculated for these MP using the formula [13]:

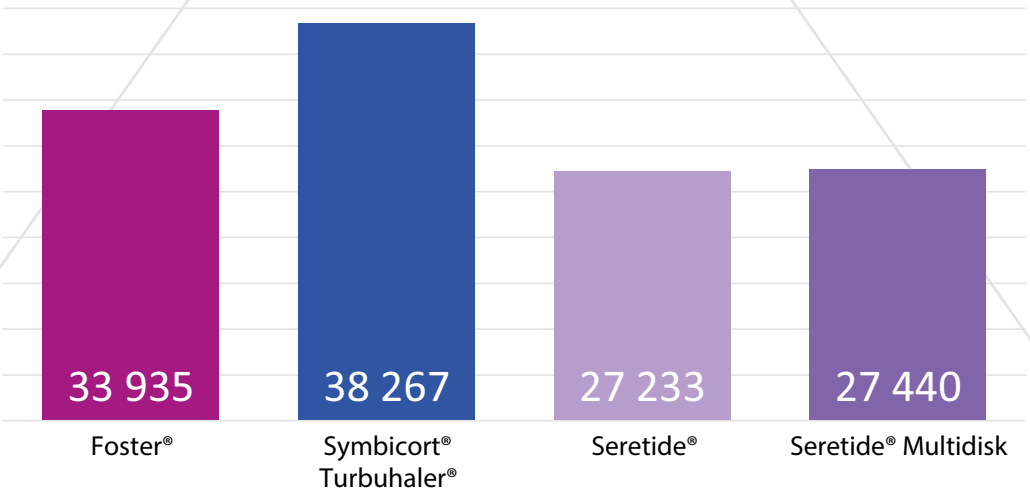

Figure 1. Results of the cost-utility analysis with reference to QALY, RUB.

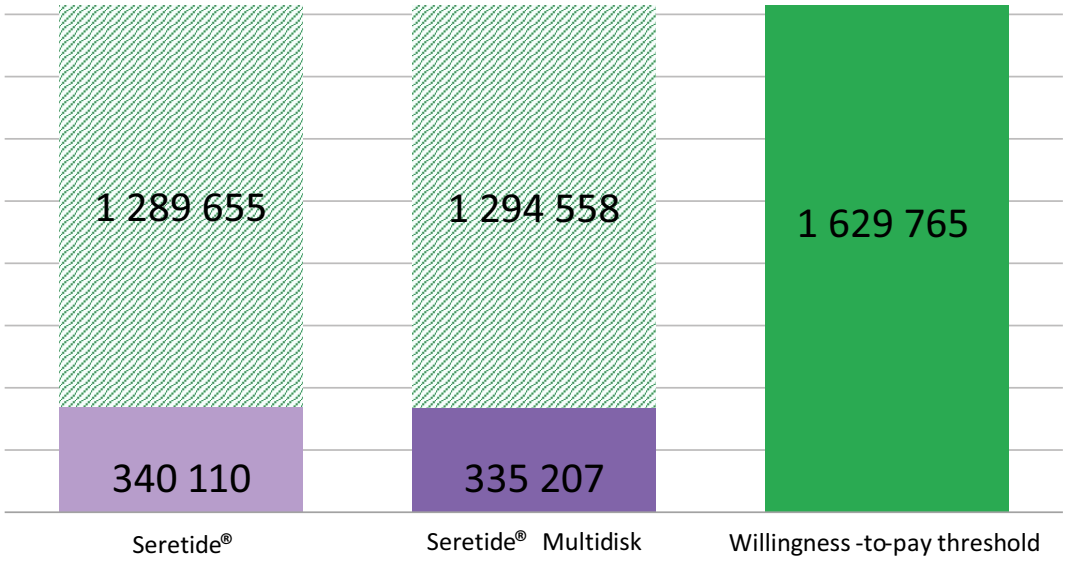

Figure 2. Results of the incremental cost-utility analysis, RUB

$$ICUR = \frac{Cost_1 - Cost_2}{Ef_1 - Ef_2}, \quad (2)$$

where ICUR is the incremental cost-effectiveness ratio;

$Cost_1$, $Cost_2$ are the costs of Foster® and Seretide®/Seretide® Multidisk, respectively, RUB;

Ef_1, Ef_2 is the effectiveness value of Foster® and Seretide®/Seretide® Multidisk, respectively.

The calculations determined that achieving an additional QALY with a more effective MP Foster® requires additional outlays equal to RUB 340,110 and RUB 335,207 compared to Seretide® and Seretide® Multidisk, respectively (Figure 2). When comparing ICUR to the willingness-to-pay threshold (WPT) in the Russian Federation, RUB 340,110 (3×GDP per capita), it was determined that the outlay for achieving an additional effectiveness unit is lower than WPT for Russia, which makes it possible to conclude that Foster® is cost-effective for treatment of BA patients.

Budget impact analysis

The next stage of the study was the budget impact analysis [14] to evaluate the economic impact on the healthcare system budget considering the number of BA patients when selecting the therapy with fixed combinations BDP/FOR, BUD/FOR, FP/SAL. This study analyzed the time interval of use of the options under comparison equal to one year, in accordance with the recommended instructions for use. According to the statistical data of MH RF, the number of BA patients in the Russian Federation is 1,072,554.

We analyzed two hypothetical situations related to the proportion of the options under comparison on the market. The following final results were obtained from the budget impact analysis (Table 5).

Table 5. Results of the budget impact analysis of BA treatment
Number of BA patients in the Russian Federation: 1,072,554.

Trade name	Current variant of distribution, % of patients	Model variant of distribution, % of patients
Foster®	3.8	25
Symbicort® Turbhaler	61.4	25
Seretide®	17.8	25
Seretide® Multidisk	17	25
Cost difference, RUB:	1,618,738,126	

The budget impact analysis demonstrated that transferring additional 21% of Russian asthma patients to the combination of beclometasone dipropionate and formoterol is characterized by the cost difference equal to RUB 1,618,738,126, compared to the combinations budesonide/formoterol and fluticasone propionate/salmeterol, provided that patients had been distributed in the following proportion: 3.8% (Foster®), 61.4% (Symbicort® Turbuhaler®), 17.8% (Seretide®), 17% (Seretide® Multidisk).

Conclusions

The pharmacoeconomic analysis of the use of Foster®, Symbicort® Turbuhaler®, Seretide®, and Seretide® Multidisk in pharmacotherapy of bronchial asthma established the following:

1. On the basis of the effectiveness analysis conducted, it can be concluded that the use of Foster® for treatment of BA patients makes it possible to achieve a higher quality of life compared to other combinations of IGCS/LABA and is associated with a lower incidence of exacerbations compared to Seretide® and Seretide® Multidisk, which results in a better asthma control.
2. According to the cost-utility analysis, the therapy with Foster® is dominant and characterized by the lowest cost with reference to QALY compared to Symbicort® Turbuhaler® and is cost-effective compared to Seretide® and Seretide® Multidisk on the basis of the incremental cost-utility ratios obtained, which are significantly lower than the willingness-to-pay threshold in Russia.
3. The budget impact analysis demonstrated that the use of BDP/FOR therapy results in budget savings compared to BUD/FOR and FP/SAL if an additional number of patients (21%) are transferred to Foster®.

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