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PHARMACOECONOMIC EVALUATION OF VIGAMOX (MOXIFLOXACIN) MEDICAMENT USE IN THE TREATMENT OF BACTERIAL CONJUNCTIVITIS

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Summary: *The pharmacoeconomic evaluation of the treatment of infectious bacterial conjunctivitis by the medicaments of fluoroquinolones: moxifloxacin (Vigamox), levofloxacin (Oftaquix, Signicef), ciproflaxacinum (Cipromed) and ofloxacin (Floksal) have been conducted in regards to the conditions of the Russian health care system. The results of analysis of the «cost-effectiveness» have shown that the medicament of moxifloxacin (Vigamox) is dominant over the comparator medicaments, requiring the least cost to achieve the successful treatment of bacterial conjunctivitis per patient. The «budget impact» analysis have illustrated that the replacement of the fluoroquinolone medicament of the II-III generation for the moxifloxacin (Vigamox) in the treatment of bacterial conjunctivitis is accompanied by cost savings.*

Keywords: *pharmacoeconomic studies, infectious bacterial conjunctivitis, fluoroquinolones, moxifloxacin, levofloxacin, ciprofloxacin, ofloxacin, analysis of the «cost-benefit», "budget impact» analysis.*

The infections of the anterior eye occupy a leading position in the structure of morbidity in the ophthalmic practice. This group of diseases includes various disease entities: blepharitis, keratitis, keratoconjunctivitis, conjunctivitis, uveitis, and others. The most epidemiological significance of all these diseases is preserved for the conjunctivitis [2, 3].

The conjunctivitis is an inflammation of the mucous membrane of the eye - conjunctiva. The share of conjunctivitis accounts for over half of all cases of infectious diseases of the anterior segment of the eye [2,3]. Etiologically we differentiate bacterial, viral and allergic conjunctivitis; from the standpoint of disease conjunctivitis is divided into the acute and chronic types.

The economic burden for conjunctivitis and other infectious diseases of the anterior eye is determined by the structure of costs in the treatment. In accordance with the costs, the treatment of conjunctivitis and other communicable diseases in the anterior segment of the eye is characterized by a relatively low cost of pharmacotherapy and other direct medical costs, as well as by the indirect costs due to significant time disability and distraction of economically active patients' relatives from their work to care for them. So, the 80 % of cases of temporary disability and 50% of hospitalizations from all infectious diseases of the anterior segment of the eye are connected to the conjunctivitis [2]. The economic evaluation of the treatment of conjunctivitis in the United States has shown an average cost of $589 million [5]. In Russia there's no cost analysis for the conjunctivitis disease.

The list of medicines (drugs) for the treatment of infectious diseases of the anterior eye and conjunctivitis, in particular, includes a wide range of antimicrobials. In Russian medical practice there are both commonly used medicines, such as sodium sulfatsil, and modern antimicrobial agents, such as fluoroquinolones.

Thus, it seems relevant to settle the objective of conducting pharmacoeconomic evaluation of treatment of infectious diseases of the anterior eye in the conditions of the Russian health care in order to create an optimal profile of medicine supply in this category of patients, both from the standpoint of therapeutic efficacy and economic feasibility [4, 6, 7]. The latter conditions are particularly important and indispensable for deciding on the optimal pharmaceutical care from the perspective of the health care system of the Russian Federation, since this system operates within a limited budget, which requires rational use of available resources.

Given the number of disease entities within the group of infectious diseases of the anterior eye, and even more medicines used in their treatment, it was decided to specify the subject matter of pharmacoeconomic studies. The purpose of the pharmacoeconomic analysis was to evaluate the treatment of the acute bacterial conjunctivitis infective medicines of the fluoroquinolones in terms of practical public health of the Russian Federation. The selection of the fluoroquinolones, as an object of the analysis, was due to the fact that this group of medicines most commonly are used in the treatment of bacterial conjunctivitis and contains a large range of topical medicaments. Fluoroquinolones are bactericidal antibiotics that disrupt DNA synthesis by inhibiting the enzyme topoisomerase. As reference medicaments in the pharmacoeconomic study there were examined the fluoroquinolones medicament of the II-IV generations following the example of International Nonproprietary Names (INN) of trade names (TN) (Table 1) [16].

Table 1. *INN and TN in the pharmacoeconomic study.*

International Nonproprietary Names	Generation Antibiotics	Trade names (producer)
Ofloxacin	II generation	Floxal (Bausch and Lomb)
Ciprofloxacin	II generation	Cipromed (Promed Exports)
Levofloxacin	III generation	Oftaquix (Santen) Signicef (Promed Exports)
Moxifloxacin	IV generation	Vigamox (Alcon)

Possessing close pharmacodynamic characteristics, the representatives of different generations of fluoroquinolones have differences in the spectrum of antibacterial activity and pharmacokinetic characteristics. Thus, a fourth-generation fluoroquinolone medicine is active in a number of strains of bacteria resistant to the earlier fluoroquinolones. From the position of the pharmacokinetics, the moxifloxacin has superior penetration and distribution structures in the anterior segment of the eye [16].

The described study was conducted using the following methods of pharmacoeconomic analysis [4,6,7]:

- analysis of the «cost-effectiveness»;
- "budget impact» analysis;
- modeling;
- method of expertise.

Within the described pharmacoeconomic study the opportunities of the modeling method were widely used: the study was carried out as a pharmacoeconomic model in the software product of the MS Excel. The need to use the simulation (modeling), as well as the method of expert opinion was dictated by a number of objective factors, characterizing the disease itself and, especially, its treatment in the Russian health care. The following findings are of high importance.

✓ Dynamism of epidemiology and its pathogens: in divers regions at different time intervals dominate various strains of pathogens.

✓ Variability in the antibiotic resistance in bacterial strains of pathogens conjunctivitis.

✓ Lack of domestic clinical studies comparing the analyzed medicines in the treatment of bacterial conjunctivitis by hard points (% of successfully treated patients).

✓ Incorrectness of the application of foreign clinical studies on the effectiveness of medicaments considered in Russia (because of different strains of pathogens abroad and in Russia).

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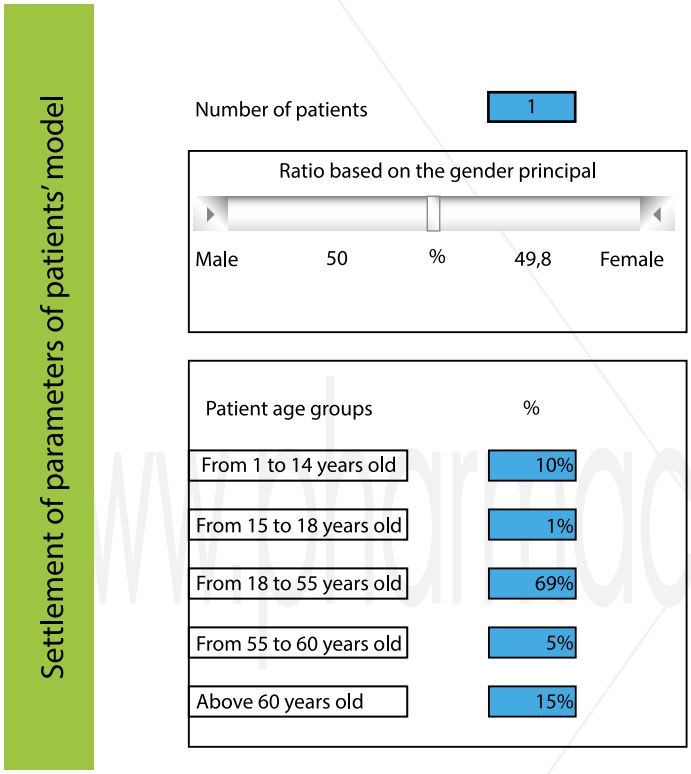
✓ In the real medical practice for treating bacterial conjunctivitis in Russia the predominance of empirical approach in the selection of antibiotic therapy, resulting in a lack of adequate systematic national data on the epidemiology of pathogens of bacterial conjunctivitis in Russia and the effectiveness of antibiotic medicament therapy.

✓ Significant loss of mass of data on the effectiveness of treatment and consequences of self-treatment of bacterial conjunctivitis due to patients.

The developed pharmacoeconomic model takes into account all of the above features of the treatment of bacterial conjunctivitis. The model has been developed for the next patient profile: male and female aged between years (Fig. 1). In view of the fact that in the model the acute conjunctivitis has been considered, its time horizon does not exceed one month, and no discounting has been performed [8].

Figure 1. Inputs: setting parameters of a patient



Analysis of effectiveness

In connection with the above characteristics of the disease of bacterial conjunctivitis and its pharmacotherapy in the model of synthetic indicator evaluating the therapeutic efficacy of the compared medicaments has been developed.

As a measure of effectiveness has been selected the % option of successfully treated patients, determined for each considered medicament (the sum of products of a particular strain on the prevalence rate share for the sensitive in regard to this antibacterial agent microorganisms of the strain):

$$Ef = (100\% - \Sigma (fi * R)), \text{ where:} \quad (1)$$

Ef – efficiency;

fi - strain rate;

R-% of the strain resistant to the said antimicrobial agent.

The sources of data on the incidence of pathogens of bacterial conjunctivitis were based on the multi-center prospective study titled VIZ 2008 [3] and data of the Saint-Petersburg Branch of the Eye Microsurgery named after Academic S.N. Fyodorov [1]. The results of epidemiological analysis are presented in the Table 2. At the same time due to lack of data in the base case of the model it has been assumed to consider bacterial compositions of pathogens in conjunctivitis among adults and children as equal.

Table 2 Epidemiology pathogens of bacterial conjunctivitis.

Frequency	Bacterial conjunctivitis	
Pathogen		
	children	**adults**
S.aureus	40,40%	40,40%
Staphylococcus spp.	20,40%	20,40%
Streptococcus spp.	7,70%	7,70%
S.pneumoniae	5,40%	5,40%
H. Influenzae	4,60%	4,60%
P.aeruginosa	3,30%	3,30%
Micrococcus spp.	3,00%	3,00%

The data on resistance to pathogens of bacterial conjunctivitis investigational medicaments has been obtained from the corresponding report of the St.Petersburg branch of the Eye Microsurgery named after Academic S.N. Fyodorov in 2010, and it is presented in the Table 3.

Table 3. Resistance of pathogens strains to antimicrobial agents.

Medicament	Levofloxacin	Moxifloxacin	Ciprofloxacin	Ofloxacin
Pathogen	% of resistant strains			
S.aureus	00,00%	10,00%	19,00%	19,00%
Staphylococcus spp.	4,00%	25,00%	28,00%	25,00%
Streptococcus spp.	00,00%	10,00%	40,00%	30,00%
S.pneumoniae	32,00%	10,00%	32,00%	21,00%
H. Influenzae	32,00%	10,00%	32,00%	21,00%
Micrococcus spp.	5,00%	5,00%	21,00%	5,00%

At the next stage of the analysis of efficiency in the above procedure we calculated the % of patients with bacterial conjunctivitis who successfully responded to treatment for each medicament. The analysis of efficacy has illustrated that the moxifloxacin (Vigamox) has the highest efficiency - 94.78%, compared to alternative antibacterial agents for which this indicator is equal to 88.78%, 78.65% and 81.97%, respectively, for levofloxacin, ciprofloxacin and ofloxacin (Table 4). It's assumed as well that the efficiency of the analyzed trade names of medicines is equal to that of relevant international non-proprietary names.

Table 4. The results of the efficiency analysis

Medicament	**Moxifloxacin**	**Levofloxacin**	**Ciprofloxacin**	**Ofloxacin**
% of patients successfully responding to treatment				
Conjunctivitis	94,78%	88,78%	78,65%	81,97%

Cost analysis

The implemented cost analysis took into account the costs of direct and indirect costs. The direct costs included the cost of antibacterial agents, the cost of concomitant pharmacotherapy, costs of diagnostic procedures, hospitalization and treatment of complications. The model of patient movement forming the basis of the "cost-benefit analysis" was based on the expert opinion in order to improve its adequacy in regards to the real practice. According to the used model of patient movement, the latter necessarily required a visit to the ophthalmologist and assignment of one of the analyzed antibacterial medicines. The overwhelming majority of patients (99%) received empirical antibiotic therapy with antibiotics in the form of eye drops, and only 1% of patients was prescribed to the laboratory microbiological diagnosis. Also, 99% of patients in the model received outpatient treatment and only 1% of them required hospitalization, the duration of which was 5 days.

In the case of treatment failure, defined on the basis of the analysis of efficiency, all patients were prescribed to the laboratory microbiological diagnosis and were offered to move from one antibacterial agent to another class (with fluoroquinolones to aminoglycosides (tobramycin)). In terms of the treatment

failure, the rates of hospitalization increased to 5%, and there was a risk of complications of bacterial conjunctivitis-keratoconjunctivitis (0.65% of patients, not responding to treatment) and corneal ulcers (0.20 % of patients not responding to treatment).

The indirect costs were determined by the frequency of writing out a sheet of temporary disability, which according to experts, in regards to the first time visit to the doctor was 5% (temporary disability duration was 7 days) and 10% in terms of the treatment failure (Table 5.).

Table 5. Model of patient movement

Frequency of prescribing sheet of temporary disability and its validity in the first call to the doctor	5,00%
	7 days
Frequency of prescribing sheet of temporary disability and its validity in the treatment failure	10,00%
	7 days
The frequency and duration of hospitalization in the first call to the doctor	1,00%
	5 days
Frequency and duration of hospitalization for the treatment failure	5,00%
	5 days
Frequency of the empirical antibiotic therapy	99,00%
The incidence of complications as:	
Conjunctivitis	0,00%
Keratoconjunctivitis	0,65%
Keratitis	0,00%
Corneal ulcer with the treatment failure	0,20%

In the scopes of the analysis of costs the retail prices for medicines were taken into account. As a source of information about the prices of medicines was used the registry for prices (if the drug is included in the VED (among the studied antibacterial agents - Vigamox (moxifloxacin) of the Alcon company, Tsipromed (ciprofloxacin) of the Promed company and Signicef (levofloxacin) of Promed)) [12] and data of the electronic resource aptechka.ru (for all other medicaments) [9]. The data source on the cost of medical services included the pricelists of the Eye Microsurgery Center named after Academic S.N. Fyodorov, and medical centers of the First MSMU named after I.M. Sechenov [13,14]; the prices for diagnostic procedures were determined by the pricelist of the Invitro company [11]. The calculation of the indirect costs was carried out on the basis of data on population, GDP and per capita income of the Federal State Statistics Service [10].

Due to the fact that we considered only the acute conditions, the time scheme of which didn't exceed more than 1-2 weeks, it has been concluded on the need for basic studies of one bottle of each medicine, i.e. the cost of the course was equal to the cost of the vial of medicine. The cost for the course study of antibacterial medicaments is shown in the Table 6.

Table 6. Course fee for the analyzed antibacterial medicaments

International nonproprietary name	Trade names	Product type	Packing cost, in rub.	Cost of the course dose, in rub.
Moxiefloksatsin	Vigamox	Eye drops, 5ml vial-droppers N1x1 Alcon Laboratories, USA	249,50	249,50
Ciprofloksatsin	Cipromed	Eye drops 0.3%, 5 ml - vial-droppers plastic - packs cardboard - Promed Exports	143,98	143,98
Levofloxacin	Oftaquix	Eye drops 0.5% vial-droppers 5ml N1x1 Santen FIN	262,36	262,36
	Signicef	eye drops 0.5% vial-droppers formation 5ml N1x1 Promed Exports IND	262,36	262,36
Ofloxacin	Floxal	0.3% eye drops, 5ml vial Bausch and Lomb N1x1 GER	235,22	235,22

The cost of a visit to the ophthalmologist was 350 rubles. The cost of a complex diagnostic procedures was 1370 rubles (Table 7).

Table 7. Cost of the diagnostic procedures

Service Title:	Cost:
A visit to an ophthalmologist, physical check-up	350,0rub.
Swab from the conjunctival cavity	150,0rub.
Sowing on the microflora and determining the sensitivity to antibiotics (conjunctival discharge)	870,0rub.
Total	1 370,0rub.

The cost of one day for the hospital stay was 2000 rubles. The direct costs also included the cost of treating complications of the treatment failure. These complications included keratoconjunctivitis and corneal ulcer. The cost of treating keratoconjunctivitis per patient was 2 000.59 rubles and included: conducting diagnostics (1370 rubles), the appointment of local reparative medicines (184.43 rubles - a combination of medicaments of glycosaminoglycans, dexpanthenol, methylethylpyridinol, carbomer), nonsteroidal anti-inflammatory medicaments in the form of eye drops (226.9 rubles – medicament of indomethacin) and replacing of antibiotics (219.26 rubles – medicament of tobramycin). The cost of the treatment of corneal ulcers was calculated on the basis of a draft standard posted on the website of the Russian ophthalmologists' community [15], and it constituted 32 882.33 rubles per patient.

The indirect costs were calculated as the sum of GDP losses because of the distraction from work for a period of temporary disability caused by bacterial conjunctivitis (or care of the child with the disease) and payments for temporary disability sheets. The cost of one day of disability was 1 247.60 rubles.

The total treatment costs per patient with bacterial conjunctivitis was calculated by the following formula (2) and with regard to their efficiency for each of the analyzed medicines constituted, respectively, for Vigamox (moxifloxacin) 217.5 1 rubles per patient , Oftaquix (levofloxacin) - 1 310.3 rubles per patient, Signicef (levofloxacin) - 1 310.3 rubles per patient, Cipromed (ciprofloxacin) - 1 321.2 rubles per patient and 1369.4 rubles per patient for Floxal (ofloxacin) (Table 8) .

$$Total\_cost = cost\_Th + cost\_Vis + (1-p1)*(cost\_j + cost\_test) + p2*(cost\_hosp*n1) + B*p3*(cost\_incp*n2) + P*(cost\_Vis + cost\_j + cost\_test + p4*cost\_hosp*n3 + B*(p5*cost\_incp*n4 + \sum pi*cost\_compi + cost\_dexa)), \text{ where:} \quad (2)$$

Total_cost	**cost_j** Swabbing cost	**cost_hosp** costs for one hospital day	**p1** frequency of empirical therapy	**p4** frequency of hos-pitalization with treatment failure	**pi** frequency of com-plications	**n3** number of days of hospitali-zation in case of treatment failure
cost_Th Costs of the main pharmaco-therapy	**cost_test** Costs of determining sensitivity to antibiotics	**cost_compi** Costs of treatment of complexities	**p2** frequency of hospitalization at the first call to doctor	**p5** frequency of giving bulletin sheets in case of treatment failures	**n1** number of days of hospitalization at the first call to doctor	**n4** number of sick days in treatment failures
cost_Vis cost of the physical check-up	**cost_incp** daily costs for disability	**cost_dexa** Costs of dexamethasone	**p3** Frequency of issuing bulletin sheets at the first visit to doctor	**P** frequency of failures of treatment	**n2** number of sick days in treatment failures at the first visit to doctor	**B** share of economically active population in the group of patients

Table 8. Results of cost-analysis

Medicaments	Vigamox	Oftaquix	Signicef	Cipromed	Floxal
Direct costs, in rub.	820,6	869,1	869,1	808,4	880,4
Indirect costs, in rub.	396,9	441,2	441,2	512,8	489,0
Total costs, in rub.	1 217,5	1 310,3	1 310,3	1 321,2	1 369,4

Analysis of the «cost-effectiveness»

After the analysis of the effectiveness and cost-benefit analysis we carried out pharmacoeconomic analysis of the «cost-effectiveness». As a measure of «cost-effectiveness» was used the successful treatment cost per patient (the cost of successful treatment of 1% of patients multiplied by 100) with bacterial

conjunctivitis. The calculation of the «cost-effectiveness» was made based on the following formula:

$$CER = \frac{Cost}{Ef}$$, where: (3)

CER – the factor of the «cost-effectiveness»;

Cost – the cost of medical technology, in rub.;

Ef – the indicator of the effectiveness of medical technology.

The calculated value of 1 successfully treated patient for Vigamox (moxifloxacin) was 1285 rub., for Oftaquix and Signicef (levofloxacin) - 1479 rub., for Cipromed (ciprofloxacin) - 1680 rub. The treatment for Floxal (ofloxacin) – 1671 rub. (Table8).

Table 8. Results of the analysis of «cost-effectiveness»

Moxifloxacin	Levofloxacin		Ciprofloxacin	Ofloxacin
Vigamox	Oftaquix	Signicef	Cipromed	Floxal
CER – the indicator of the «cost-effectiveness» of cost for the 1 successfully treated patient				
1 285 rub.	1 479 rub.	1 479 rub.	1 680 rub.	1 671 rub.

Budget-impact analysis

In the scopes of pharmacoeconomic studies we also carried out the "budget-impact" analysis, which allowed determining the net economic effect of the impact on the budget in regards of replacement of one medicament to another. The selection of this method of pharmacoeconomic analysis was dictated by the advantages of Vigamox medicine in terms of its efficiency in combination with a lower value of total costs at which the incremental analysis of the "cost - utility» had no mathematical sense (as the incremental cost- utility ratio acquires a negative value). The results of the "budget impact" analysis were expressed by the difference of total economic effects of the two medicaments. The total economic effect of the treatment was expressed by the total costs for treatment of bacterial conjunctivitis per patient by each of the tested medicaments. In the present study, based on the results of the "cost –analysis" it was revealed that the replacement of Oftaquix, Signicef, Tsipromed and Floksal on Vigamox saved per patient respectively 92.9 rub., 92.9 rub., 103.8 rub. and 151.9 rub. for the health care system budget.

Findings

Thus, in the scopes of the pharmacoeconomic study the following results have been obtained. The efficiency analysis conducted on the first phase of this study demonstrated an advantage of the Vigamox medicament in comparison with compared medicines in the treatment of bacterial conjunctivitis: Vigamox was effective in 94.78 % of patients, while the effectiveness Oftaquix, Signicef, Cipromed and Floxal, respectively, constituted 88.78 % , 88, 78 % , 78.65 % and 81.97 %.

Resulting from the cost-benefit analysis it was found that the cost of treating one patient with bacterial conjunctivitis with the medicaments of Vigamox, Oftaquix, Signicef, Cipromed and Floxal respectively constituted 1 217.5 rub., 1 310.3 rub., 1 310.3 rub., 1 321.2 rub. and 1 369.4 rubles. The total costs for the treatment of bacterial conjunctivitis with the Vigamox medicament were low in comparison with those for Oftaquix and almost equal in comparison with Signicef, Tsipromed and Floksal. At the same time the appointment of Vigamox allowed to reduce the indirect costs, which accounted 397 rub. per patient for Vigamox, and for comparator medicaments ranged from 441 to 513 rub.

The analysis of the budget impact revealed that the Vigamox medicament was a reducing costs agent compared with the medicamets of Oftaquix, Signicef, Tsipromed and Floksal in the treatment of bacterial conjunctivitis, providing 92.9 rub., 92.9 rub., 103.8 rub. and 151.9 rubles for the cost savings per patient, respectively, compared with Oftaquix , Signicef, Tsipromed and Floksal.

It was found that the treatment of bacterial conjunctivitis with Vigamox had a dominant position within the analysis of «cost-effectiveness» since in the best therapeutic efficacy Vigamox compared with the other medicaments had the lowest value of the indicator of «cost-effectiveness «, which was adopted for the cost of a successfully treated patient. So, for Vigamox this indicator was 1285 rub., and for Oftaquix, Signicef, Floksal and Tsipromed it was, respectively, 1479 rub., 1479 rub., 1680 rub., 1671 rub. Thus, Vigamox actually has achieved a successful outcome of antibacterial therapy of conjunctivitis with least means in comparison with medicaments-competitors and could be attributed to the group of strongly preferred medicaments.

Conclusion

The conducted pharmacoeconomic study revealed that the treatment of bacterial conjunctivitis with Vigamox (moxifloxacin) had an advantage in comparison with the medicaments of Tsipromed (ciprofloxacin), Oftaquix, Signicef (levofloxacin) and Floksal (ofloxacin) at a rate of the «cost-effectiveness», and it's the dominant one. From the standpoint of the «budget impact analysis» the replacement of compared medicaments with Vigamox was accompanied by net budget savings of the health system.

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