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- МЕТОДОЛОГИЧЕСКИЕ АСПЕКТЫ ПРОВЕДЕНИЯ ФАРМАКОЭКОНОМИЧЕСКОГО ИССЛЕДОВАНИЯ ТЕРАПИИ СПАСТИЧЕСКИХ ФОРМ ДЕТСКОГО ЦЕРЕБРАЛЬНОГО ПАРАЛИЧА
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- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

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PHARMACOECONOMIC ASSESSMENT OF THE USE OF DALBAVANCIN (XYDALBA) IN THE TREATMENT OF SKIN AND SOFT TISSUE INFECTIONS IN HOSPITAL SETTINGS IN THE RUSSIAN FEDERATION

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Summary: *This article is devoted to the evaluation of the use of dalbavancin (Xydalba) in the treatment of skin and soft tissue infections in hospital settings in the Russian Federation. The main methods of pharmacoeconomic analysis in the study were the following: cost-minimization analysis and budget impact analysis. The results of the pharmacoeconomic evaluation of dalbavancin treatment of patients with skin and soft tissue infection in Russia hospitals showed its stable advantage from the point of view of cost analysis and budget impact analysis in comparison with telavancin and tigecycline. The results of the cost-minimization analysis indicate of the dominance of dalbavancin in comparison with telavancin. At the same time, a comparative cost-minimization analysis of dalbavancin and tigecycline showed the advantage of the former, which, however, is not preserved when assessing the stability of the results through a one-factor sensitivity analysis with an increase in the price of dalbavancin by 15%. In accordance with the quantitative assessment of clinical and economic effectiveness, regulated by Decree of the Government of the Russian Federation N871 dated August 28, 2014, dalbavancin obtains +8 points on the pharmacoeconomic criterion.*

Key words: *pharmacoeconomic analysis, clinical and economic analysis, "cost minimization" analysis, "budget impact" analysis, dalbavancin, telavancin, tigecycline*

A review of publications on the global burden of disease analysis shows that for the world health this century is considered as the era of "non-infectious epidemics" [1-4]. Thus, according to the results of a global burden of disease study, coordinated by the Institute for Health Metrics and Evaluation [5], the top 10 causes of death in the world in 2015 included seven noncommunicable diseases and only two infectious diseases; in 1990, among the ten most common causes of premature death, five were infectious diseases. However, despite the breakthrough in the treatment of infectious diseases, many experts are afraid of the return of the problem of infectious diseases, especially in the field of treatment of bacterial diseases [6-7]. Mainly, this is due to two factors (in addition to widespread use of antibiotics in agriculture): development of resistance in infectious agents to existing medicines and the slowing down of the development of new anti-infectious agents [7-14].

Thus, there is an increase in the prevalence of strains of bacteria possessing multiple drug resistance. Annually more than 700 thousand deaths are registered because of infections caused by treatment-resistant pathogens [14]. At preservation of existing dynamics it is predicted that by 2050 the number of annual deaths due to infectious diseases caused by treatment-resistant pathogens will increase to 10 million, and global economic losses for the period 2015-2050 may amount to more than 100 trillion dollars [14]. This problem is especially relevant for nosocomial or hospital infections [15-16]. Among the antibiotic-resistant pathogens of nosocomial infections, S. aureus, Enterococci, Pseudomonas spp., Acinetobacter spp., Pseudomonas aeruginosa [16] are of greatest importance. A study of nosocomial infections in the United States showed that the incidence of methicillin-resistant Staphylococcus aureus (MRSA) increased from 3% in the 1980s to 53% in the 2000s [16]. Cases of infections caused by pathogens that are not susceptible to treatment have been reported [17]. Separately it is necessary to emphasize that the problem of treatment of infectious diseases caused by resistant pathogens, being a global threat to public health, is also relevant for Russia [18, 34].

On the other hand, the share of medicines for the treatment of infectious diseases among all drugs under development in 2015 did not exceed 20% [19]. According to other data, as of March 2016, 37 potential antibacterial drugs are under development in pharmaceutical companies, while only 11 are in phase I studies [20]. While the number of developed drugs, for example, in the field of oncology in 2015 was more than three hundred [21]. From the point of view of the volume of resources invested by pharmaceutical companies in the development of new drugs, researchers note that for the period 2003-2013, drugs for the treatment of infectious diseases accounted for about $ 1.8 billion of $ 38 billion, or only 4.7% [14].

In this regard, the emergence in the pharmaceutical market of new anti-infectious agents, including antibacterial drugs, should be considered as a valuable opportunity to expand the possibilities of pharmacotherapy for infectious diseases.

Registration in 2017 in Russia of a new antibacterial medicinal product from the group of glycopeptide antibiotics - dalbavancin (Xyidalba, Angelini Farma Rus) for the treatment of skin and soft tissue infections, on the one hand, may be an important option for improving the quality of medical care in case of corresponding infectious diseases, and on the other hand, sets the task of ensuring the availability of a new medication for patients. One of the main elements of ensuring the availability of medicines in Russia after their state registration is the inclusion in the list of drugs and, in particular, in the list of VED. The rules for including medicinal products in the relevant lists are regulated by RF Government Decree N871 dated August 28, 2014, including the requirements for the provision of data on the pharmacoeconomic (clinical and economic) evaluation of the medicinal product within the framework of the proposal [22]. For this reason, the pharmacoeconomic analysis of the use of dalbavancin in the treatment of bacterial infections in patients with infections of the skin and soft tissues in the Russian public health environment was considered relevant. This article is devoted to the description of the results of the pharmacoeconomic study.

The aim of this study was to conduct a pharmacoeconomic evaluation of treatment in a hospital of infectious diseases of the skin and soft tissues with dalbavancin.

The subject of the study of pharmacoeconomic analysis was the antibacterial drug dalbavancin, which according to the instructions for use is indicated for the treatment of skin and soft tissue infections caused by MRSA [18]. Taking into account the significance of MRSA among nosocomial infections, the model of patients in the described pharmacoeconomic analysis included patients with skin and soft tissue infection that was caused by MRSA. In addition to dalbavancin, the following drugs registered in Russia have the same indication for medical use: telavancin, tigecycline, daptomycin, ceftarolin, linezolid, and vancomycin. From this list of medicines, telavancin and tigecycline were chosen as reference drugs.

In addition to the fact that these drugs have a corresponding indication for medical use, both drugs of comparison are modern original drugs (telavancine was registered in Russia in 2015, tigecycline in 2009) [23], therefore, they can be comparable in terms of economics, which is important for an adequate pharmacoeconomic assessment. It is very important for pharmacoeconomic analysis to use medications that are comparable in time of development, since the comparison of innovative drugs with drugs that were developed several

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decades ago (like vancomycin) can obviously be inadequate, which is due to the initially different level of investment in the development of new drugs and, accordingly, the level of prices for medicines. Since the advent of vancomycin, the average cost of a new medicinal product development has almost tripled, now amounting to more than $ 2 billion [24].

The evaluated drugs dalbavancin and telavancin belong to the same class of antibiotics - glycopeptides, while drug tigecycline is a representative of tetracyclines. Consequently, the comparator drugs used can determine the pharmacoeconomic profile of dalbavancin within the same pharmacological group as well as allow an intergroup evaluation of the innovative drug. Thus, in the present study, a pharmacoeconomic assessment of the use of dalbavancin in hospital in comparison with telavancin and tigecycline in the treatment of skin and soft tissue infections caused by MRSA was conducted (Table 2).

Table 2. Comparator drugs included in the pharmacoeconomic analysis

INN	TN	MA Holder	Pharmaceutical form	Date of MA issue
Telavancin	Vibativ	R-Pharm	Liofilizate, 750 mg - vials (1)	June 18, 2015
Tigecycline	Tigacil	Pfizer	Liofilizate, 50 mg - vials (10)	October 13, 2009

Efficacy Analysis Results

In the course of the information search, no clinical studies were found in which a statistically significant advantage of one of the compared drugs over another would be concluded. It should also be noted that the Bayesian approach meta-analysis of Logman JF et al. 2010 [25] suggests a higher success rate with dalbavancin and new glycopeptides, though did not reveal significant differences between the studied drugs, and in this connection, in the present pharmacoeconomic study, it was assumed that the clinical efficacy of the compared drugs was equal. In this connection, in the future, the "cost minimization" analysis was used as one of the types of cost-effectiveness analysis. Also, due to the lack of a proven difference in efficacy between the drugs being compared and, consequently, the same level of success / failure of treatment (the need for changing the antibiotic), the time horizon of the described pharmacoeconomic study was limited by the course of antibacterial therapy with the drugs studied.

Cost Analysis Results

In the conducted pharmacoeconomic study, direct and indirect costs were taken into account [26-27]. At the first stage of the cost analysis, the course costs for the treatment with the drugs studied of one patient with infections of the skin and soft tissues caused by MRSA were calculated in hospital settings. For this purpose, at the beginning, the cost per a unit of active ingredient of each drug was determined. At the same time, the averaged tender prices for 2016 for telavangin and tigecycline calculated on the basis of the public procurement portal data were used [28] (Table 3).

Table 3. The price for a package of telavancin and tigecycline by the results of tenders

Medicinal Product	Price per a package, rub.
Telavancin	11,874.18
Tigecycline	2,295.49

Since dalbavancin was registered in Russia only in 2017 and therefore did not participate earlier in procurement, its cost was calculated on the basis of the price of import to Russia provided by the manufacturing company and was reduced to the wholesale price by accounting for customs duties, wholesale surcharges, and VAT (Table 4).

Table 4. Calculation of the drug packaging price dalbavancin

Price Type	Price, rub.
Manufacturer's import price	24,900
Price with the cost of customs clearance (3.25%) 3% duty and 0.25% customs clearance	25,709
Wholesale service charge (+10%)	28,280
inc VAT price (+10%)	31,108

The cost per unit of active ingredient based on the price per package and the amount of active ingredient in the drug package for dalbavancin, telavancin, and tigecycline was 62.22 rubles, 15.83 rubles, 52.59 rubles, respectively.

After determining the cost per unit of active ingredient of each of the medicines, the costs of dalbavancin, telavancin, and tigecycline were calculated for the course of treatment for one patient.

Dalbavancin:

62.22*1500 = 93,324 rub.

Telavancin[1]:

15.83*9800 = 155,155.95 rub.

Tigecycline:

52.59*1400 = 73,627.37 rub.

Since all considered drugs are injected, the cost of medical services for intravenous administration has been taken into account in the calculations. At the same time, the cost of the injection was taken from the price list of City Clinical Hospital No. 13 in Moscow [29] and amounted to 400 rubles. Therefore, direct medical costs for the administration of dalbavancin amounted to 400 rubles, and for telavancin, and tigecycline to 5600 rub. Also, in the conducted cost analysis, direct nonmedical costs were taken into account - the cost of a bed-day amounted to 1000 rub. [29]. Then the cost of staying in a hospital for treatment of a patient with telavancin or tigecycline with a course duration of antibiotic therapy of 14 days is 14,000 rubles. When treating infections of the skin and soft tissues with dalbavancin, the patient is given one injection corresponding to one day of hospitalization. Given the time needed to achieve the patient's recovery, required for the patient to be discharged from the hospital, duration of patient's stay in the hospital from the beginning of prescribing antibiotic therapy to discharge when using dalbavancin was 5 days. Thus, the cost of staying in a hospital with the prescription of dalbavancin is 5000 rubles.

Thus, the total direct exchange costs for the treatment of skin and soft tissue infection by dalbavancin, telavancin, and tigecycline were 98,724 rubles, 174,756 rubles, and 98,827 rubles, respectively (Figure 1). At the same time, the costs for dalbavancin were less than those for telavancin and tigecycline, respectively, for 43.5% and 0.1%.

At the final stage of the cost analysis, indirect costs related to GDP losses and payment of temporary disability sheets for patients in the hospital were calculated [27]. The source of information on the GDP value and the average monthly wage was the statistical data of the Federal State Statistics Service. It should be noted that in the ongoing pharmacoeconomic study, it was assumed that patients of an average age of 50 years with a skin and soft tissue infection caused by MRSA were treated. Indirect costs due to loss of GDP per patient were as follows:

On dalbavancin:

(551,919 / 365) * 5 = 7,560.53 rub.

On telavancine and tigecycline:

(551,919 / 365) * 14 = 21,169.5 rub.

Indirect costs associated with payment of temporary disability sheets were calculated per patient:

On dalbavancin:

(33,981 / 30.5) * 0.8) * 5 = 4,456.52 rub.

On telavancine and tigecycline:

((33,981 / 30.5) * 0.8) * 14 = 12,472.27 rub.

The total costs for the treatment of one patient with infection of the skin and soft tissues caused by MRSA in hospital conditions were 110,741 rubles, 208,404 rubles, and 132,475 rubles, respectively, with the use of dalbavancin, telavancin, and tigecycline. (Figure 2).

Results of the cost-minimization analysis

Cost-minimization analysis implies determination of the least expensive alternative and is based on the assumption of equal effectiveness of the investigational drugs [27]. In the cost-minimization analysis direct costs were considered. As a result of the cost-minimization analysis it was found that, per patient, the use of dalbavancin is accompanied by a saving of money in

[1] Since the dose of telavancin is calculated based on the patient's body weight, in the present pharmacoeconomic study, it was assumed that the average weight of patients was 70 kg.

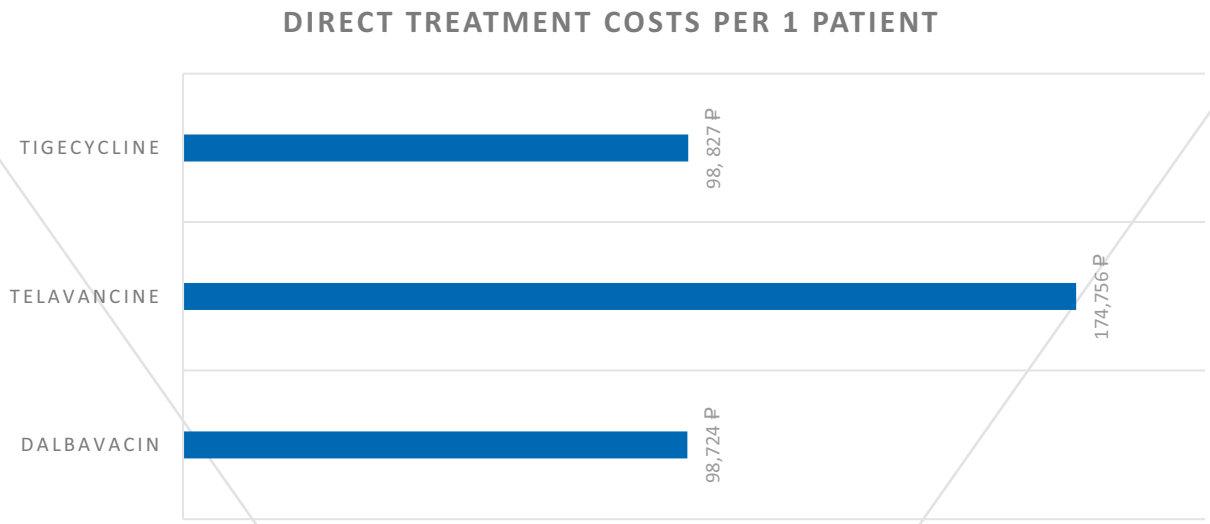


Figure 1. Direct costs of antibiotic therapy of skin and soft tissue infections per patient.

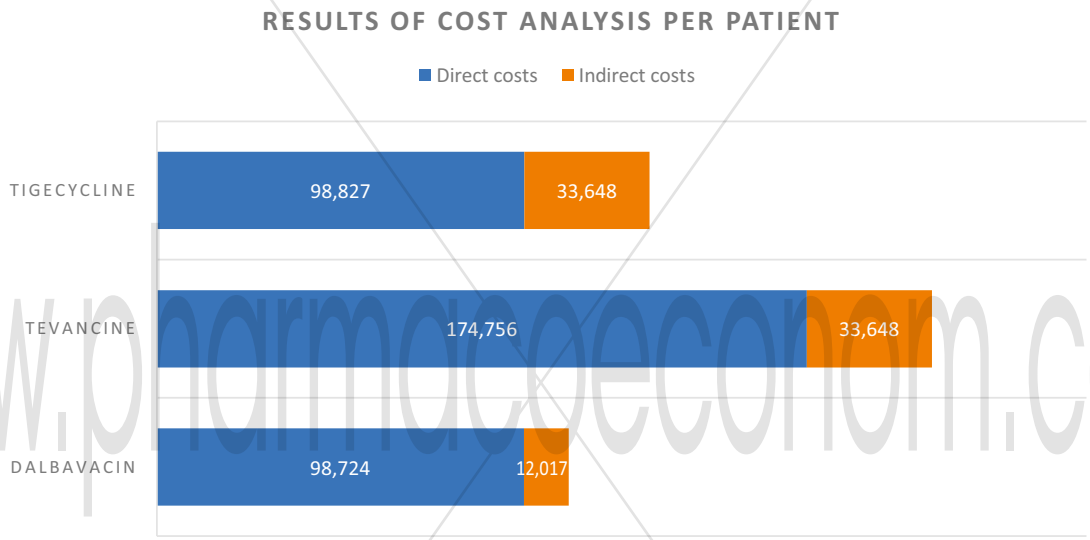
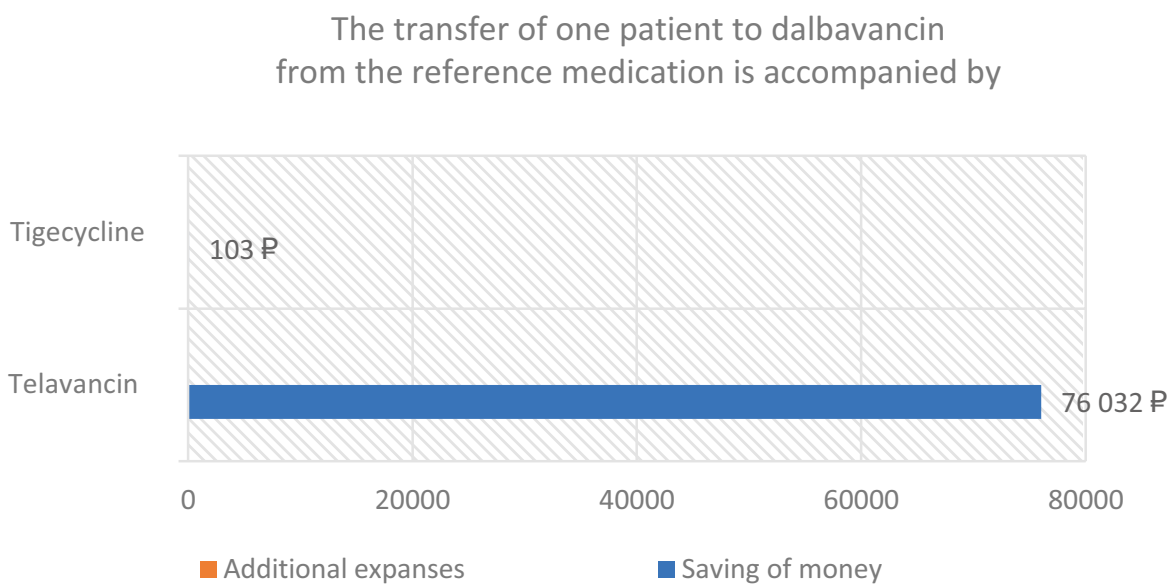


Figure 2. Cost Analysis Results



the amount of 76,032 rubles. In comparison with telavancin and 103 rubles in comparison with tigecycline (Figure 3).

Figure 3. Results of the cost-minimization analysis

Results of the budget impact analysis

An analysis of the budget impact analysis [30] showed that, based on one patient, the use of dalbavancin in the treatment of skin and soft tissue infections caused by MRSA under stationary conditions provides a savings of 97,663 rubles in comparison with telavancine and 21,734 rubles in comparison with tigecycline.

In the "budget impact" analysis, a scenario assessing the inclusion of a new medicinal drug dalbavancin in the practice of treating skin and soft tissue infections in Russia, taking into account the distribution of patients between antibiotic regimens was also considered [31]. According to the data of the marketing agency IMS-health [32] in 2016, 4,279 patients with infections of the skin and soft tissues were treated with telavancin (3%) or tigecycline (97%). Based on the data presented above, the total direct and indirect costs for the treatment of the specified number of patients in the distribution of 2016 are 576.6 million rubles. We modeled the situation in which a new drug dalbavancin will be prescribed to 37% of patients (as this level of patients eligible for early discharge was observed in EU (33)). The total budget, including direct and indirect costs, for the treatment of 4,279 patients with a modeled distribution of patients (37% in dalbavancin, 1% in telavancin, and 62% in tigecycline) amounted to 535.7 million rubles. Thus, the savings in the simulated distribution are 40.9 million rubles. (Figure 4).

132,475 rubles for dalbavancin, telavancin, and tigecycline respectively. Thus, the conducted cost analysis showed that the use of dalbavancin in the treatment of infections of the skin and soft tissues is characterized by a lower value of both direct and indirect costs in comparison with telavancin and tigecycline.

Cost-minimization demonstrated that, per patient, the use of dalbavancin is accompanied by savings of 76,032 rubles in comparison with telavancin and 103 rubles in comparison with tigecycline. Thus, dalbavancin is characterized by the advantage from the position of the cost-minimization analysis.

Budget impact analysis carried out within the framework of the pharmacoeconomic study showed that, based on one patient, the use of dalbavancin in the treatment of skin and soft tissue infections caused by MRSA under hospital conditions provides saving of 97,663 rub. (46%) in comparison with telavancin and 21,734 rub. (16.4%) in comparison with tigecycline. Also, during the budget impact analysis," it was revealed that the transfer of 37% of 4276 patients receiving telavancin or tigecycline to dalbavancin would be accompanied by savings of 40.9 million rubles.

The single-factor sensitivity analysis performed on the variable parameter of the cost per package of dalbavancin showed stability of the obtained results of the pharmacoeconomic evaluation. Only the comparison of dalbavancin

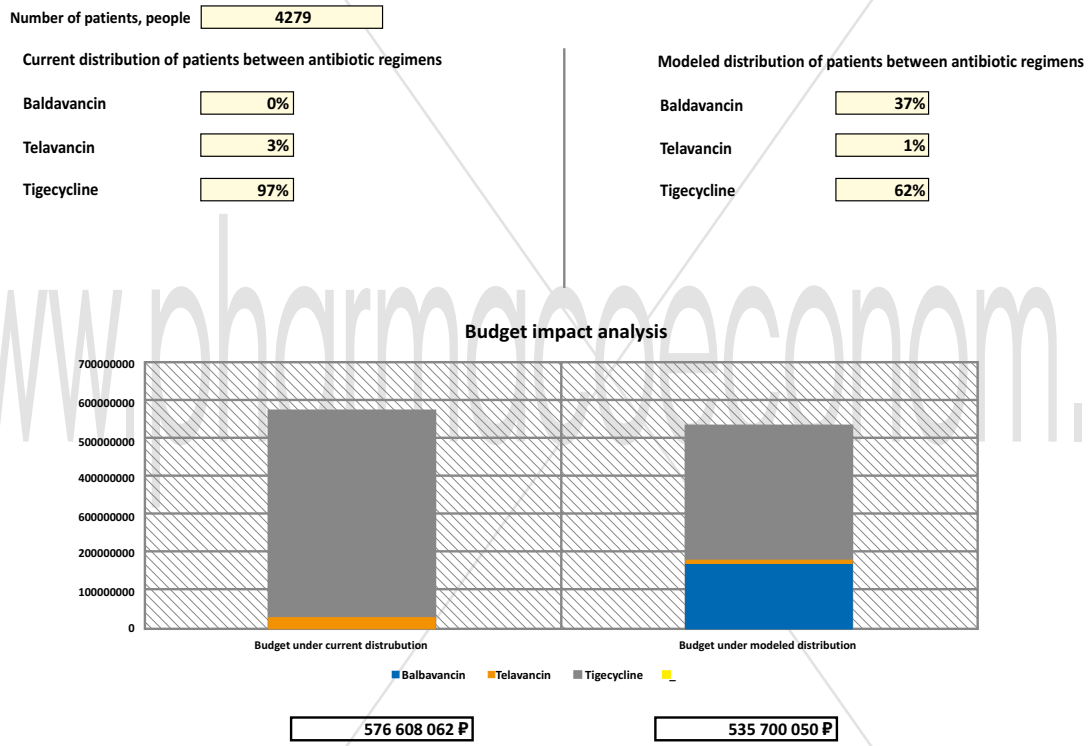


Figure 4. Results of the budget impact analysis

Discussion:

As part of the information search conducted, no studies have been found that indicate of a statistically significant difference in the efficacy of treatment of skin and soft tissue infections between dalbavancin, telavancin, and tigecycline. However, due to its dosing regimen, in which the course dose can be injected at a time with a single injection, dalbavancin allows a significant reduction in the duration of stay in the hospital, which contributes to an increase of efficacy in the use of hospital beds, on the one hand, and reduces the risk of re-infection, on the other hand.

It has been demonstrated already that reduced length of stay in hospital decreases the cross-colonization of nosocomial infections; (33)The direct exchange costs calculated in the course of the cost analysis for the treatment of skin and soft tissue infection by dalbavancin, telavancin, and tigecycline amounted to 98,724 rubles, 174,756 rubles, and 98,827 rubles. At the same time, the costs of dalbavancin were less than those for telavancin and tigecycline, respectively, for 43.5% and 0.1%. The total costs for the treatment of one patient with infection of the skin and soft tissues caused by MRSA in hospital conditions were 110,741 rubles, 208,404 rubles, and

with tigecycline in the context of the "cost minimization" analysis failed sensitivity analysis.

Conclusion:

The results of the pharmacoeconomic evaluation of dalbavancin treatment of patients with skin and soft tissue infection in Russia hospitals showed its stable advantage from the point of view of cost analysis and budget impact analysis in comparison with telavancin and tigecycline. The results of the analysis of "minimization of costs" indicate of the dominance of dalbavancin in comparison with telavancin. At the same time, a comparative analysis of the "minimization of costs" of dalbavancin and tigecycline showed the advantage of the former, which, however, is not preserved when assessing the stability of the results through a one-factor sensitivity analysis with an increase in the price of dalbavancin by 15%. In accordance with the quantitative assessment of clinical and economic effectiveness, regulated by Decree of the Government of the Russian Federation No. 871 dated August 28, 2014, dalbavancin obtains +8 points on the pharmacoeconomic criterion with the required minimum of +4 points [22].

References:

1. Sidney C. Smith. Reducing the Global Burden of Ischemic Heart Disease and Stroke. A Challenge for the Cardiovascular Community and the United Nations. Circulation. 2011;124:278-279.
2. ATLAS of DIABETES IDF Seventh Edition, 2015. - 144 P.
3. Dr. Otis Brawley. Most cancers in our world pandemic are preventable - here's how. CNN [electronic resource], access mode: http://edition.cnn.com/2014/02/04/health/brawley-cancer-tips/
4. American Society for Cancer Research [electronic resource], access mode:
5. https://www.cancer.org/research/infographics-gallery/rising-global-cancer-epidemic.html
6. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Volume 388, No. 10053, p1459–1544
7. The global threat of antimicrobial resistance: science for intervention. I. Roca, M. Akova, F. Baquero, J. Carlet, M. Cavaleri, S. Coenen, J. Cohen, D. Findlay, I. Gyssens, O.E. Heure, G. Kahlmeter, H. Kruse, R. Laxminarayan, E. Liébana, L. López-Cerero, A. MacGowan, M. Martins,18 J. Rodríguez-Baño, J.-M. Rolain, C. Segovia, B. Sigauque, E. Taconelli, E. Wellington, and J. Vila. New Microbes New Infect. 2015 Jul; 6: 22–29.
8. C. Lee Ventola. The Antibiotic Resistance Crisis. Part 1: Causes and Threats. P T. 2015 Apr; 40(4): 277–283.
9. Peter Roskam. Reinvigorating The Antibiotics Pipeline. http://www.forbes.com/sites/realspin/2014/07/29/reinvigorating-the-antibiotics-pipeline/#45a12d9d7a51
10. Elizabeth Sukkar. Why are there so few antibiotics in the research and development pipeline? The Pharmaceutical Journal 13 NOV 2013
11. Race against time to develop new antibiotics. Bulletin of the World Health Organization. Volume 89, Number 2, February 2011, 81-160
12. Sandeep Kumar Gupta, Roopa P. Nayak. Dry antibiotic pipeline: Regulatory bottlenecks and regulatory reforms. J Pharmacol Pharmacother. 2014 Jan-Mar; 5(1): 4–7.
13. Stuart B. Levy. Factors impacting on the problem of antibiotic resistance. J Antimicrob Chemother (2002) 49 (1): 25-30.
14. Hiroshi Nikaido. Multidrug Resistance in Bacteria. Annu Rev Biochem. 2009; 78: 119–146.
15. Tackling drug-resistant infections globally: final report and recommendations. The review on Antimicrobial resistance. May 2016.
16. Robert A. Bonomo. Multiple Antibiotic-resistant Bacteria in Long-term-care Facilities: An Emerging Problem in the Practice of Infectious Diseases. Clin Infect Dis (2000) 31 (6): 1414-1422.
17. Nele Brusselaers, Dirk Vogelaers, Stijn Blot. The rising problem of antimicrobial resistance in the intensive care unit. Annals of Intensive Care 20111:47
18. Ransdell Pierson,Bill Berkrot. U.S. health officials on Thursday reported the first case in the country of a patient with an infection resistant to a last-resort antibiotic
19. V.V. Gostev, S.V. Sidorenko. Methicillin-resistant staphylococcus aureus: The problem of spreading in the world and in Russia.
20. Adis R&D Insight Database. Accessed March 2016.
21. http://www.pewtrusts.org/~/media/assets/2016/05/antibiotics-currently-in-clinical-development.pdf
22. http://m1.wyanokecdn.com/154294cceb75a0f83401b139bc08edf7.pdf
23. Decree of the Government of the Russian Federation dated August 28, 2014 No. 871 "On approval of the rules for the formation of lists of medicinal products for medical use and the minimum range of medicines required for the provision of medical care"
24. State Register of Medicines. Date of application: February 26, 2017.
25. Congressional Budget Of ce (CBO). A CBO study: research and development in the pharmaceutical industry. Access mode: www.cbo.gov/sites/default/ les / cbo les / ftpdocs / 76xx / doc7615 / 10-02- drugr-d.pdf.
26. Comparative effectiveness of antibiotics for the treatment of MRSA complicated skin and soft tissue infections. Logman JF, Stephens J, Heeg B, Haider S, Cappelleri J, Nathwani D, Tice A, van Hout BA. Curr Med Res Opin. 2010 Jul;26(7):1565-78.
27. Yagudina R.I., Serpik V.G. The methodology of cost analysis // Pharmacoeconomics: Theory and practice. - 2016. - V.4, No.2. - P.5-9
28. Yagudina R.I., Kulikov A.Yu., Serpik V.G. Pharmacoeconomics: Textbook - Rostov n / a: Feniks, 2017. - 237 p.
29. Unified information system in the field of procurement. Access mode: www.zakupki.gov.ru date of application is 27.02.2017.
30. The price-list of City Clinical Hospital No. 13 of the DZ of Moscow. Access mode: http://gkb13.ru/services/tsenyi/ date of application – 16.02.2017.
31. Yagudina R.I., Serpik V.G., Ugrekhelidze D.T. Methodological bases of the analysis of "influence on the budget" // Pharmacoeconomics: Theory and practice. - 2015. - V.3, No.4. - P.5-8.
32. Yagudina R.I., Serpik V.G. Methodological bases of pharmacoeconomic modeling // Pharmacoeconomics: Theory and practice. - 2016. - V.4, No.1. - P.7-12
33. Data of the agency IMS-health Jan 2016
34. Eckmann Christian Antibiotic treatment patterns across Europe in patients withcomplicated skin and soft-tissue infections due to meticillin-resistantStaphylococcus aureus: A plea for implementation of early switch andearly discharge criteria International Journal of Antimicrobial Agents 44 (2014) 56–64
35. Antimicrobial resistance surveillance in Europe 2015. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). www.ecdc.europa.eu