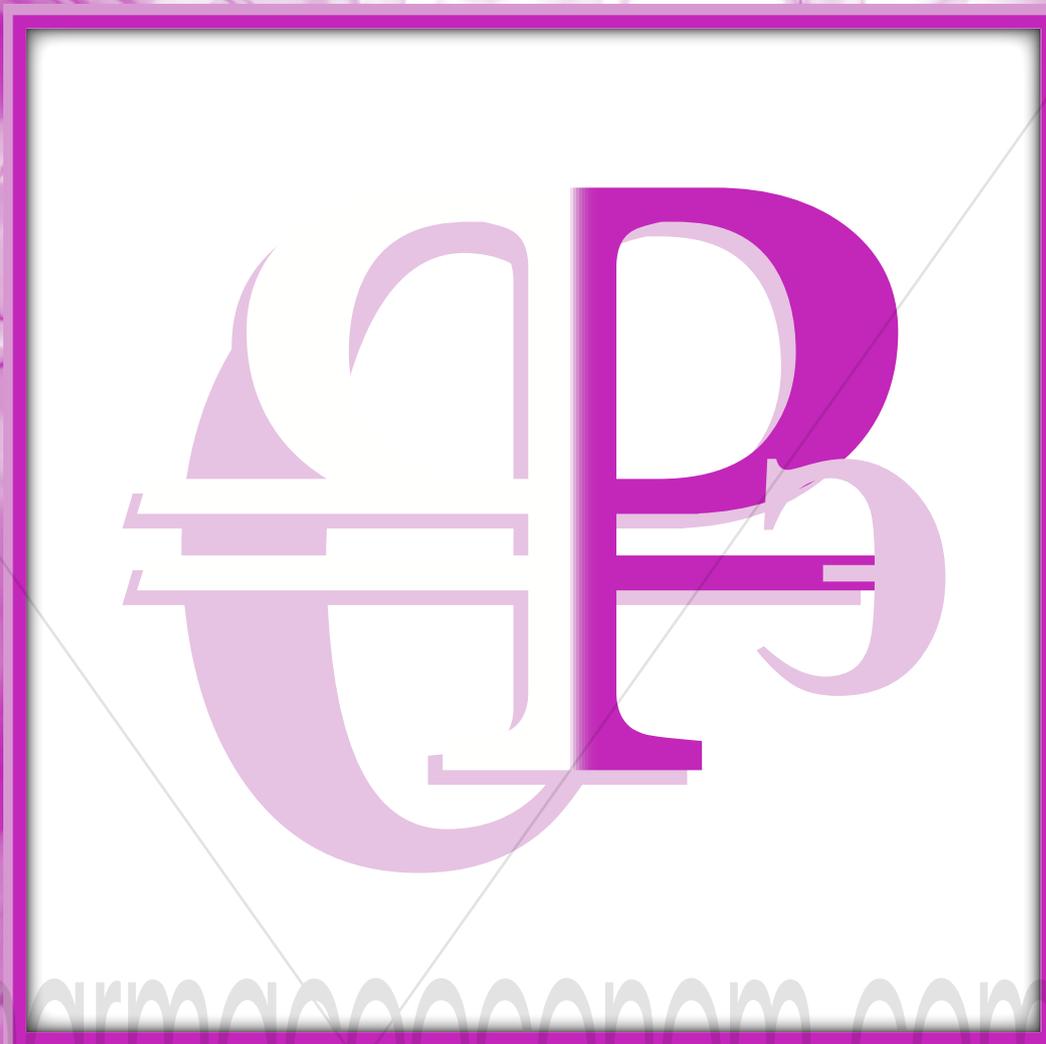


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- **IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ»**  
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- **ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ**

## PHARMACOECONOMIC EVALUATION OF RARE DISEASE MANAGEMENT IN PRIMARY MYELOFIBROSIS TREATMENT WITH RUXOLITINIB

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**Summary:** Orphan drugs designed for rare disease management is a special group of drugs from the perspective of the pharmacoeconomic analysis being a mandatory part of any proposal for inclusion in the Restrictive lists. Thanks to unique opportunities offered by orphan drugs for rare disease management through acting at the pathogenetic level, these drugs have high social significance. But inherently high cost of these innovative drugs associated with their narrow market limited due to small target population, precludes from using the conventional pharmacoeconomic approach which involves comparison of pharmacoeconomic indicators — results of cost-effectiveness and budget impact analyses — of the innovative drug vs. current medical treatment (or palliative treatment in case of no treatment option available). As such, the authors have investigated the special pharmacoeconomic approach — “precedential” — in case of ruxolitinib in treatment of primary myelofibrosis. This approach implies comparison of the studied drug vs. other orphan and high-cost medicinal products included in the National drug lists. As a result, it has been shown that the pharmacoeconomic indicators of ruxolitinib are not higher than the same of the drugs included in the Essential Drug List.

**Key Words:** pharmacoeconomics, incremental cost-effectiveness analysis, budget impact analysis, “precedential” approach, agnogenic myeloid metaplasia, rare disease, orphan drug, ruxolitinib.

According to the RF Government Regulation No. 871 dated August 28, 2014 On approval of procedure for medications and required drug listing [1], the pharmacoeconomic evaluation has become a mandatory part of any proposal to include medicinal products for human use in the lists. Based on applicable global and domestic procedures for medicine provision, the pharmacoeconomic analysis proved to be an effective tool for decision making ensuring the optimized use of healthcare scarce resources. Besides, the pharmacoeconomic analysis demonstrates a well-developed methodology which allows to consider various special features of the research objects and subjects – diseases and health care methods [7].

One of the most isolated groups of the pharmacoeconomic analysis requiring a special pharmacoeconomic approach is orphan drugs – the medicines used to treat rare diseases. The rare (orphan) diseases are those with prevalence of not more than 10 patients per 100,000 people [4]. The area of rare disease management is characterized with introduction of effective innovative drugs (and absence of any effective specific therapy in the previous period) and high prices for these drugs. According to the Federal Law On

drug circulation [3], orphan drugs are medicinal products designed only for diagnostics or pathogenetic treatment (targeted at the disease mechanism) of rare (orphan) diseases. Studying orphan drugs under the procedure for inclusion in the drug lists according to the RF Government Regulation No. 871 dated August 28, 2014, special factors of clinical studies should be noted — the limited number of patients caused by naturally low prevalence rate affecting the accuracy and credibility of the efficiency and safety evaluations of orphan drugs<sup>1</sup>. The high cost of the medicinal products designed to treat rare diseases are caused by the narrow market. Due to small target patient groups, the manufacturer has to sell the drugs at high prices to return investments in development and production and to gain profits. At the same time, the high price for the drugs of this group leads to significant decrease of their affordability essentially eliminating the opportunity for treating rare diseases with innovative drugs at the expense of the patients. In this respect, the decision must be made to include orphan drugs in Restrictive lists to exploit all emerging opportunities in the rare disease management. But due to the mentioned above specific features of orphan drugs, they can hardly be approved to be compensated for as viewed from the conventional pharmacoeconomic analysis implying calculation and further comparison of pharmacoeconomic indicators for two or more alternative health care methods. In the vast majority of cases, the cost for the life year added or quality adjusted life year added for orphan drugs is much higher than the “willingness to pay” threshold adopted for all healthcare systems globally and according to the budget impact analysis, there are substantial additional expenses which have to be incurred to introduce orphan drugs into clinical setting especially when compared with obsolete and low-cost drugs for symptomatic treatment [5]. (Figure 1).

However, it should be noted that there is an approach in pharmacoeconomic analysis allowing for sounder factoring in the speciality of rare diseases when making decisions about inclusion in the national lists. This approach is known as “precedential” [16-18], and according to it, the pharmacoeconomic indicators calculated for orphan drugs are compared not with the available healthcare methods but with the results of pharmacoeconomic evaluation of the method included in the national lists. The “precedential” approach is based on fairness and equality of rights according to which if patients with a disease get drug with a certain pharmacoeconomic profile for free (reimbursement) within this healthcare system (precedent-setting), there are no grounds to deprive reimbursement the patients with other diseases which are treated with other drugs with a pharmacoeconomic profile equal

<sup>1</sup> It is reflected in Government Regulation No 871 dated 28.08.2014 commencing a special evaluation rule for clinical efficiency of the orphan drugs. Eventual results.



to the same of the “precedent-setting” drug. An example of precedential approach use in the international practice was demonstrated by Great Britain when it was decided to compensate costs for expensive and orphan drugs [14] based on the previous experience of paying compensations for drugs having incremental cost-effectiveness ratio exceeding the “willingness to pay” threshold established in Great Britain. Currently, the “precedential” approach to pharmacoeconomic evaluation of orphan drugs is neither defined nor prohibited by the RF Government Regulation No. 871 dated August 28, 2014. In this respect, the authors introduce a case study of “precedential approach” use to conduct pharmacoeconomic analysis for orphan drug ruxolitinib using for treatment of myelofibrosis.

Primary myelofibrosis (PMF, chronic idiopathic myelofibrosis, myelofibrosis with myeloid metaplasia, subleukemic myelosis, chronic granulocytic megakaryocytic myelosis) proceeds de novo. PM is characterized with clonal proliferation of stem cells, abnormal cytokine expression, bone marrow fibrosis, hepatosplenomegaly due to extra medullary hemopoiesis, tumor intoxication symptoms, cachexia, leukoerythroblastosis of peripheral blood, leukemia progression, and low survival rate [6]. According to different sources, MF incidence varies within the range of 0.1 – 1 patient per 100,000 people. Thus, the estimated amount of Russian patients is about 1,400 persons that meet the criterion of rare diseases [15]. MF management methods may be classified as follows:

- Allogeneic hematopoietic stem cell transplantation (allo- HSCT);
- Surgical management (splenectomy);
- Radiation therapy;
- Hemocomponent treatment;
- Drug therapy.

Allo-HSCT is the only method capable to ensure complete cure of a patient but having a number of limitations, mainly availability of the eligible donor and a patient’s condition. The limitations prevent from using this method for all patients are in need. Other treatment methods including surgery, radiation and hemocomponent therapy, administration of cytostatic drugs (hydroxycarbamide, cytarabine, mercaptopurine, busulfan), interferon alfa, epoetin, glucocorticoids and androgens (nandrolone, metandienone, danazol) are symptomatic. Development of ruxolitinib (Jakavi®, Novartis Pharma LLC) [8], belonging to tyrosine kinase inhibitors, opened up the possibility for pathogenetic treatment of MF allowing for better disease management and improvement of prognosis for patients with MF. Thus, ruxolitinib therapy for patients with MF can be interesting from the perspective of “precedential” pharmacoeconomic evaluation.

At the first stage of the pharmacoeconomic analysis, the respective pharmacoeconomic indicator – an incremental costs-effectiveness ratio – was

calculated and the budget impact from ruxolitinib introduction in the clinical setting was defined taking into account the penetration factor of the study drug. The pharmacoeconomic analysis was conducted for a one-year time horizon; a quality-adjusted life year (QALY) was used as an effectiveness criterion; as per expenses, direct treatment charges were considered. Based on the clinical recommendations for PMF management, combined administration of hydroxycarbamide and interferon was selected as an alternative method to ruxolitinib therapy [6].

Life expectancy and quality data were obtained for each of the investigated alternative method through information search. Due to the specificity of the disease under study, we have found out one multicentral randomized study comparing ruxolitinib therapy vs. the best available therapy2. According to Harrison C. et al. [13], the QALY at the therapy week 48 reached 4.1 for ruxolitinib while for the best available therapy, QALY was 2.82.

Annual treatment costs were calculated for each treatment regimen based on average registered marginal prices [8] for hydroxycarbamide and interferon drugs and ruxolitinib price according to the price-list3. Besides, the calculations are based on the following dosage regimen: ruxolitinib — 30 mg per day, hydroxycarbamide — 20 mg/kg of body weight per day (an average body mass was assumed as 70 kg), interferon alfa – 2.5 mln units once every other day. Annual treatment costs for a patient were RUB 2,642,547 for ruxolitinib and RUB 122,004 for the combined hydroxycarbamide and interferon therapy.

At the next stage of the pharmacoeconomic analysis, the incremental costs-effectiveness ratio was calculated according to formula (1) based on the data on effectiveness and costs of the compared alternative PMF treatment regimens. This ratio reflects the cost of one added QALY for more effective method [7].

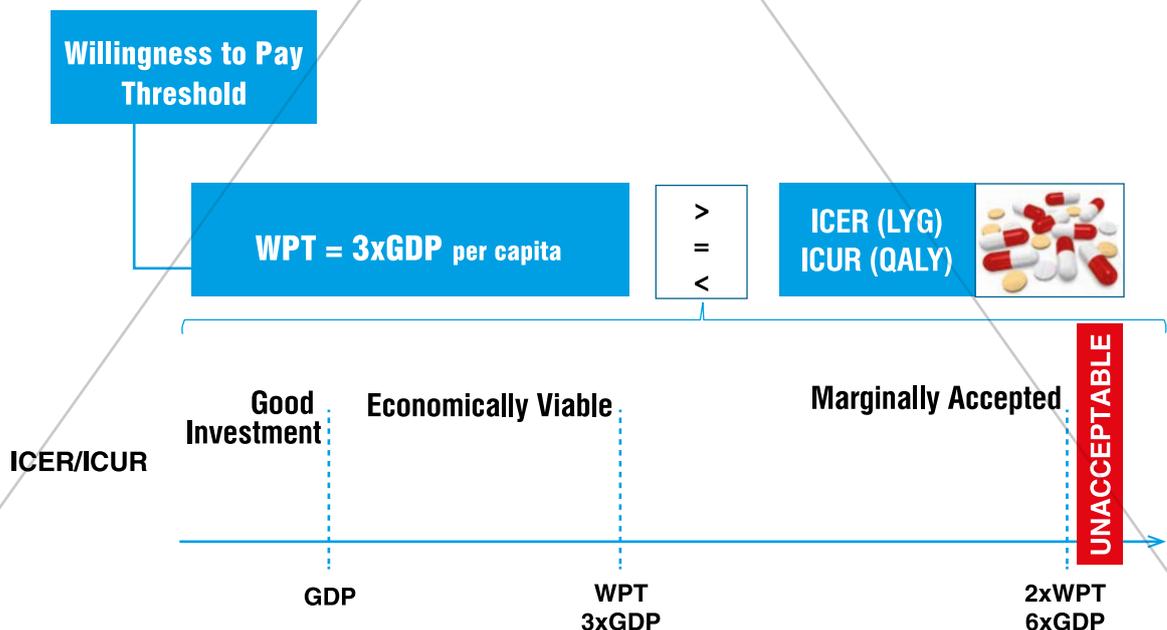
$$ICUR = \frac{Cost(1) - Cost(2)}{Ut(1) - Ut(2)} \text{ или } \frac{Cost(1) - Cost(2)}{\Delta Ut}, \text{ where (1)}$$

ICUR – incremental costs-effectiveness ratio; Cost (1), Cost (2) – costs for the studied and standard treatment methods respectively, RUB;

Ut(1), Ut(2) – effectiveness indicators for the studied and standard treatment methods respectively, QALY.

The incremental costs-effectiveness ratio was RUB 1,812,848 per one added QALY. The calculated incremental costs-effectiveness ratio was compared with the “Willingness to pay” threshold which was defined as a tripled GDP per capita per year amounting to RUB 1,395,513. It was shown the incremental costs-effectiveness ratio for ruxolitinib is higher than the “Willingness to pay” threshold but lower than the doubled “Willingness to pay” threshold. Thus, Ruxolitinib therapy for PMF may be deemed as marginally acceptable as viewed by the “conventional” pharmacoeconomic approach.

Figure 1. Method evaluation within pharmacoeconomic analysis



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Besides, the pharmacoeconomic analysis has defined the budget of ruxolitinib therapy given its penetration level of 10%. This penetration level was selected with a view to innovation factor of the study drug determining gradual introduction of a novel drug into clinical setting. The annual budget of ruxolitinib therapy for 140 patients with PMF was RUB 369,962,175.

At the final stage of the pharmacoeconomic analysis, the "precedential" approach was used to compare annual treatment costs and incremental costs-effectiveness ratio for ruxolitinib vs. other drugs [2, 8]:

- Eculizumab (Soliris), an orphan drug included in the vital and essential medicines list and purchased according to the regional reimbursement program;
- Eptacog alfa (Coagil VII), used to treat hemophilia, included in the high-cost drug list

- Fludarabine (Fludara), used to treat oncohematological diseases, included in the expensive drug list.

The annual costs were compared for ruxolitinib vs. eculizumab and eptacog alfa therapy. Annual eculizumab treatment cost RUB 25,895,168 per patient (based on average auction price; dosage regimen according to the Prescribing Information) while annual costs for eptacog alfa therapy per one patient were RUB 24,930,012 (Figure 2) [8, 9, 11].

The incremental costs-effectiveness ratio was compared for ruxolitinib vs. eculizumab and fludarabine. The incremental costs-effectiveness ratio of eculizumab was about RUB 41,375,750 per one added QALY (the value derived based on the relevant pharmacoeconomic indicator calculated for Great Britain and converted into rubles) [9, 14], and RUB 2,990,851 for fludarabine [12].

Figure 2. Cost of annual treatment with the study drugs

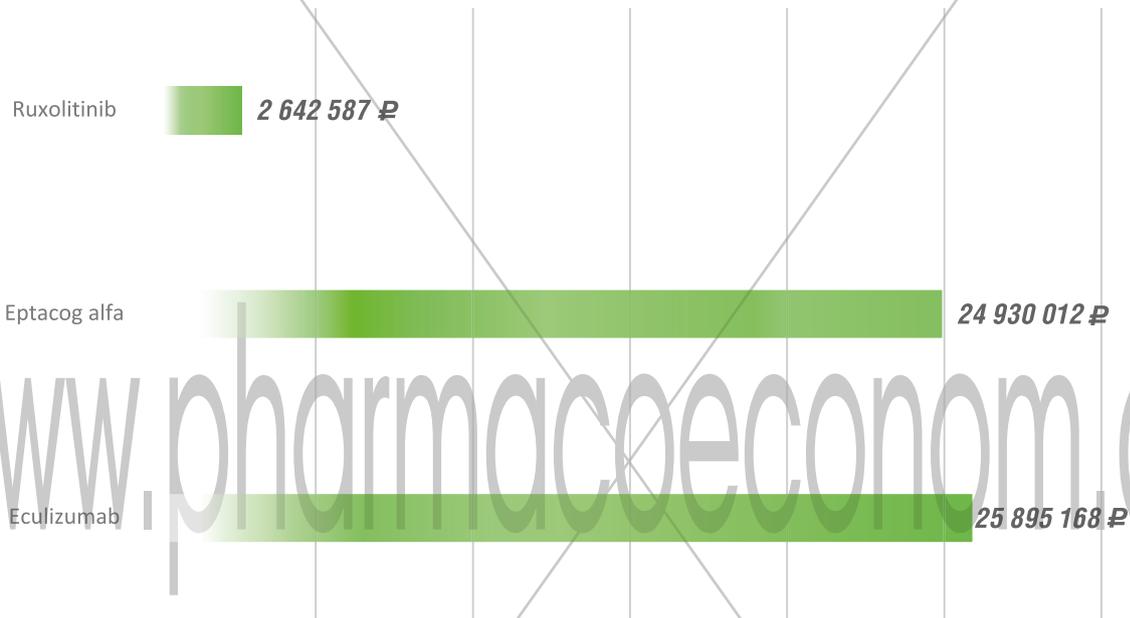
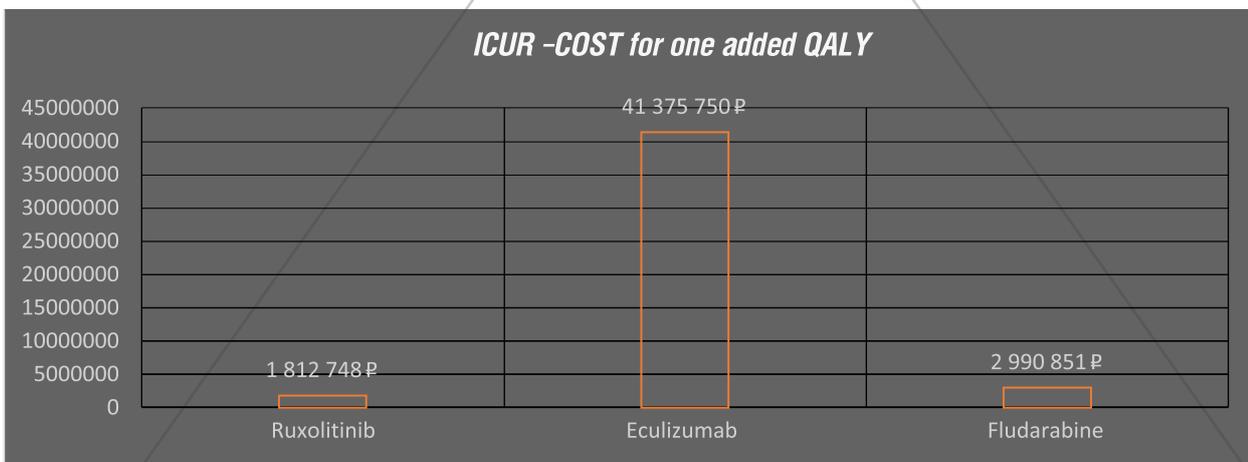


Figure 3. Incremental cost-effectiveness ratio for the drugs under study



<sup>2</sup> It was assumed that the best affordable therapy included hydroxycarbamide and interferon.

<sup>3</sup> The price for a Jakavi 15 mg package was RUB 202,719 and Jakavi 5 mg package - RUB 123,033.



Based on the data provided, ruxolitinib demonstrates both lower annual expenses and lower incremental costs-effectiveness ratio compared to the drugs already included in the national drug lists. In this respect, there are no grounds for refusing to include ruxolitinib in the national lists based on the pharmacoeconomic criterion.

### Conclusions

According to the "precedential" approach, the incremental costs-effectiveness ratio of ruxolitinib is appeared to be significantly lower than the incremental costs-effectiveness ratio of another orphan drug (eculizumab) included in the vital and essential drug list. In view of the aforesaid, there are no grounds for refusing to include ruxolitinib in the national lists based on the pharmacoeconomic criterion.

From a conventional pharmacoeconomic perspective, ruxolitinib therapy for patients with PMF demonstrates the incremental costs-effectiveness ratio not exceeding the doubled "willingness to pay" threshold and is marginally acceptable.

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