

№1 <sup>Том 3</sup>  
2015

**Фармакоэкономика**  
*теория и практика*

ФФФ

**Pharmacoeconomics**  
*theory and practice*

№1 <sup>Volume 3</sup>  
2015

- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ АНАЛИЗА ЭФФЕКТИВНОСТИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ ПРИ ПРОВЕДЕНИИ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ
- IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» – «ФАРМАКОЭКОНОМИКА – 2015» 16-17 марта 2015 г., УФА, AZIMUT ОТЕЛЬ УФА

# PHARMACOECONOMIC ANALYSIS OF THE USE OF THE KUVAN DRUG PRODUCT IN PHENYLKETONURIC PATIENTS

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**Abstract:** A pharmacoeconomic study of the treatment of phenylketonuria (PKU) treatment using Kuvan drug product combined with the diet or dietary therapy alone has been conducted. It has been established that the therapy is dominant in the first case when compared to the second case because it shows better therapeutic effectiveness and is characterized by a lower cost-effectiveness ratio. It has also been determined that the addition of Kuvan to the dietary therapy requires additional costs of 11,569,761 RUB per one patient over 16 years. Despite the increase in the costs linked to the use of the new and only drug for the treatment of PKU, the overall effect on the budget will be decreased due to the low prevalence of the disease.

**Keywords:** pharmacoeconomic analysis, effectiveness, costs, cost-effectiveness analysis, budget impact analysis, phenylketonuria, phenylalanine, Kuvan, sapropterin, dietary therapy.

## Introduction

Phenylketonuria (PKU) is a challenging issue for the public healthcare system in the Russian Federation (RF) and other countries worldwide.

PKU is a genetic disease that is inherited in an autosomal recessive fashion and results in the disturbance of the amino acid metabolism. Here, up to 1% of the cases of PKU is represented by the atypical forms associated with the mutations in other genes responsible for the coding for enzymes providing the synthesis of the cofactor of phenylalanine hydroxylase tetrahydrobiopterin (BH4). The clinical presentation of the disease develops in 2–3 weeks after the birth already and the irreversible changes in the central nervous system (CNS) develop in the child by the age of six month. Progressive intellectual disability, epilepsy syndrome, and other psychoneurological disorders are characteristic for the PKU patients [14].

The occurrence of the methods for the drug treatment of PKU is of particular interest because dietary therapy is currently the main method of medical treatment. In 2007, the Food and Drug Administration of the USA (FDA) approved the Kuvan® (sapropterin) drug product (DP) that is the first medication capable of providing the body with BH4 in the PKU patients, thus making it possible to reduce the incapacitation and mortality and improve the patients' quality of life.

This DP was registered within the territory of the RF on July 15, 2014 [9]. The introduction of Kuvan into practice will lead to the growth in the costs and burden on the budget of the public healthcare system. Therefore, the need for carrying out the pharmacoeconomic analysis of the use of the dietary therapy alone in comparison with the use of Kuvan combined with the dietary therapy in PKU patients emerges.

## Research procedure

The pharmacoeconomic assessment of the treatment of PKU patients with

the Kuvan innovative drug product combined with the dietary therapy in comparison with the dietary therapy alone was performed as part of this study. These treatment regimens were used in children from 4 years to their adulthood with the initial weight of 14 kg. It was taken into account in the study that the discounting rate was 3%. It was also assumed that the dietary therapy would reduce by 25% during the use of Kuvan

Based on the above mentioned, the pharmacoeconomic study including the following methods of pharmacoeconomic analysis was performed:

- Effectiveness analysis
- Cost analysis
- Cost-effectiveness analysis
- Budget impact analysis

## Effectiveness analysis

At the first stage of the effectiveness analysis, the information retrieval was carried out, during which over ten clinical studies on the treatment of PKU with the dietary therapy alone and with Kuvan combined with the dietary therapy were obtained. In all found clinical studies, a parameter of blood phenylalanine level decrease was used as the effectiveness criterion. The data on the effectiveness of the therapy were adopted from phase III, randomized, double-blind, multicenter, placebo-controlled study by Levy H.L. et. al., 2007. 89 PKU patients (with the average age of 20 years old), of which 42 patients administered Kuvan and 47 patients administered placebo, participated in this study. It was shown that, after six weeks of treatment, the decrease in the blood phenylalanine concentration by 30% or more when compared to the initial level occurred in 44% of patients in the group that administered Kuvan and only in 9% of patients in the control group [15–17].

## Cost analysis

The next stage of the performed pharmacoeconomic study was the direct cost analysis including the estimation of the costs for medical (including diagnostic) services, drug therapy, and dietary therapy (therapeutic mixtures) [1].

When calculating the costs for the diagnostics and treatment, the standard of medical care for PKU patients, from which the information on the medical services and their frequencies was adopted, was used [3]. The costs for the diagnostic and treatment procedures were calculated based on the prices presented in the rates of the Federal Compulsory Medical Insurance Fund (FOMS) of Moscow [4, 10]. The result of this calculation has the same monetary value both for the patients who administered Kuvan combined with the dietary therapy and patients who used the dietary therapy alone and is 70,713 RUB for one patient per the treatment course. The equal value of these costs for both groups of patients is explained by the use of the standard of medical care for PKU patients, in which the medical services received by any patient with this diagnosis are listed [11,12].



In order to calculate the costs for the therapeutic mixtures, the information search was performed in the Internet resource about the range and price of the products in question [7, 8]. When calculating these costs, patient's body weight and the normal range of protein intake including phenylalanine that depends on the patient's age (Table №1) was taken into account [2]. The cost of the therapeutic mixtures was about 4,275,112 and 3,206,334 RUB in the case of the use of the dietary therapy alone and Kuvan combined with the dietary therapy, respectively, for one patient for 16 years.

**Table 1.** The cost of the daily dose of the dietary mixture depending on the age and normal range of protein intake

Age	Average weight, kg	Protein	Phenylalanine, mg/kg	Equivalent of protein in the mixture, g	Average cost of the equivalent of protein, rub
4–7 y	19.42	54 g	22,5	45,26	1 078,88
7–8 y	24.27	63 g	15	55,72	1 328,17
8–11 y	30.79	63 g	15	53,76	1 145,69
11–13 y (m)	40.70	75 g	20	58,72	1 251,32
11–13 y (f)	41.50	69 g	10	59,31	1 248,55
13–14 y (m)	48.43	75 g	20	58,40	1 263,98
13–14 y (f)	47.60	69 g	10	59,48	1 271,64
14–18 y (m)	60.22	87 g	20	62,91	1 283,44
14–18 y (f)	53.46	76 g	10	65,31	1 332,32
18–20 y (m)	69.12	87 g	20	59,35	1 210,82
18–20 y (f)	57.28	76 g	10	64,54	1 316,74

Then, for the patients who administered Kuvan, the costs for the therapy with this drug product were estimated. The cost of a pack of Kuvan 100 mg tablets No. 30 is 79,500 RUB (as on 08/02/2015) [6]. The average daily dose of the drug product is 3.5 mg/kg. On the basis thereof, it was established that the cost of Kuvan treatment of one patient until his/her adulthood was about 12,638,539 RUB.

As a result of the cost analysis, it was determined that the overall costs in the case of the use of the dietary therapy alone would be about 4,345,825 RUB, while they would increase to 15,915,586 RUB in the case of the addition of Kuvan.

#### Cost-effectiveness analysis

Cost-effectiveness analysis allows to assess comprehensively assessing the therapies under comparison in order to determine the most effective spending of the limited resources of the public healthcare system [5]. The cost-effectiveness ratio that is calculated according to the following formula is the result of this analysis:

$$CER = Cost/Ef,$$

where CER is the cost-effectiveness ratio;

Cost is the costs for the medical technology;

Ef is the effectiveness factor of the medical technology.

The cost-effectiveness ratio (CER) was 535,844 RUB for the dietary therapy alone, while it was 354,800 RUB for Kuvan combine with the dietary therapy.

Therefore, CER for the Kuvan DP combined with the diet is lower than for the dietary therapy alone; here, Kuvan has a better therapeutic effectiveness, which makes it possible to define this therapy as dominant from the viewpoint of the cost-effectiveness analysis [13].

#### Budget impact analysis

The budget impact analysis performed at the final stage of the pharmacoeconomic analysis reflects the influence of the therapy under study on the budget of the public healthcare system. The result of the budget impact analysis is expressed by the formula:

$$BIA = Efec(1) - Efec(2),$$

where BIA is the result of the budget impact analysis, in monetary terms;

Efec(1) is the total economic effect from the use of the comparison medical technology, in monetary terms;

Efec(2) is the total economic effect from the use of the medical technology under study, in monetary terms.

Based on the cost analysis, it was calculated that additional costs of 11,569,761 RUB over 16 years would be required in the case of the transfer of one patient from the dietary therapy to the treatment with the use of Kuvan and the diet [5].

#### Conclusions

1. The effectiveness analysis of PHU treatment demonstrated the advantage of the therapy with the use of Kuvan and the diet in comparison with the dietary therapy alone. In the first case, the reduction in the blood phenylalanine by 30% and more occurred in 44% of patients, while in the second case, only in 9%.
2. The overall costs in the case of the use of the diet alone are about 4,345,825 RUB, while they increase to 15,915,586 RUB when Kuvan is added to the treatment.
3. The cost-effectiveness analysis showed that the cost-effectiveness ratio was lower for the treatment with the use of Kuvan and the diet when compared to the dietary therapy alone and was 354,800 and 535,844 RUB, respectively.
4. It was established as a result of the budget impact analysis that when Kuvan was added to the dietary therapy, additional costs of 11,569,761 RUB over 16 years were required.

#### Summary

The performed pharmacoeconomic study of the treatment of PKU showed that the use of Kuvan combined with the dietary therapy is the dominant treatment method when compared to the use of the dietary therapy alone from the viewpoint of the cost-effectiveness analysis. Here, additional costs of 11,569,761 RUB per one patient over 16 years are needed during this transition from the dietary therapy to the treatment with the use of Kuvan and the diet. Despite the increase in the costs in the case of the use of the new and only drug for the treatment of PKU, the overall effect on the budget will be reduced because of the low prevalence of the disease.

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