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- ❑ МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ПРОВЕДЕНИЯ ОЦЕНКИ ДОСТОВЕРНОСТИ НАУЧНЫХ ДАННЫХ С ПОМОЩЬЮ СИСТЕМЫ КЛАССИФИКАЦИИ, ОЦЕНКИ, РАЗРАБОТКИ И ЭКСПЕРТИЗЫ РЕКОМЕНДАЦИЙ GRADE
- ❑ РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

PHARMACOECONOMICS ANALYSIS OF THE MEDICINAL PRODUCT COPAXONE-40 IN TREATING MULTIPLE SCLEROSIS

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Abstract: The treatment of multiple sclerosis (MS) is a formidable healthcare challenge the world over. Because MS is a progressive chronic disease, patients living with this diagnosis require treatment for life. The high prevalence of the disease among young people significantly affects patients' quality of life and exacerbates the socioeconomic burden of the disease. Glatiramer acetate (Copaxone) is a synthetic analogue of the myelin protein that can influence MS pathogenesis with its immunomodulatory and neuroprotective effect. Copaxone has been continuously, safely used in clinical practice for more than 20 years. In terms of tolerance of Copaxone, the main challenge has been the adverse injection reactions associated with daily subcutaneous injection of a 20 mg/mL dose of the drug. To address this, a new pharmaceutical form was developed – Copaxone 40 mg/mL, which requires subcutaneous injection only three times a week. Both dosage regimens have comparable clinical efficacy, but differ in tolerance. Use of Copaxone 40 versus Copaxone 20 was associated with 50% fewer adverse injection reactions [11]. This suggested a need to conduct pharmacoeconomic research with the goal of producing a pharmacoeconomic assessment of Copaxone 40 versus Copaxone 20. The analysis that was conducted using the “cost minimization” analysis determined that the Copaxone 40 treatment method had lower associated costs than did the Copaxone 20 treatment method. The results of a budget impact analysis indicated that, if all patients in the RF [Russian Federation] currently receiving Copaxone 20 were to switch to therapy using the drug Copaxone 40, a cost savings of 812 million roubles would result in lower adverse reaction treatment costs. These savings would be due to the 209 fewer injections per patient per year that would be achieved by prescribing Copaxone 40, and consequently, the lower number of injection reactions.

Key words: Copaxone, glatiramer acetate, multiple sclerosis, cost analysis, cost minimization analysis, budget impact analysis, pharmacoeconomics, direct costs.

Introduction

Multiple sclerosis (MS) is one of the most common central nervous system (CNS) diseases in the world. Today more than 2.3 million people on Earth [2] are living with an MS diagnosis. According to estimates from the Multiple Sclerosis International Association [*sic*: Federation], in 2013 in Russia there were already 20 to 60 patients afflicted with MS for every 100,000 people [2]. The average age of MS patients is about 30 years [2]. MS is a chronic, progressive, dysimmune neurodegenerative disease characterized by a range of clinical presentations [3]. The most common signs of MS include spastic pareses of the limb muscles, brainstem and cerebellar symptoms (double vision, dizziness, nausea, unsteady gait), dysaesthesia, impairment of the pelvic organs, etc. [4]. These and other symptoms may grow as the disease progresses. People suffering from multiple sclerosis may at first not experience any issues. But after a few years many of them will already be unable to get around without day-to-day assistance. [2]. Bearing in mind the fact that this disease occurs most often in young people leading active work and social lives, it should be noted that MS has a significant adverse impact

not only on each patient's quality of life, but also on his/her family, friends, and society as a whole.

Because MS is among a group of diseases that costs a lot to treat, in most countries the costs of treating it are subsidized [2]; Russia is one of such country. Pursuant to Federal Law 384-FZ dated 01-Dec-2014 (13-Jul-2015 version) “On the 2015 Federal Budget and the Planned 2016-2017 Federal Budget” [5], and to RF Government Decree 2782-r dated December 30, 2014 “On Approving the List of Vital and Essential Medicines for 2015, and the Lists of Medicines for Human Use and the Minimal Assortment of Medicines Required for Rendering Medical Care” (Attachment No. 3) [6], the costs of MS drug therapy are funded from the RF federal budget.

Glatiramer acetate (GA) is among those medicines, along with interferon beta, that are purchased in bulk for multiple sclerosis patients. GA is a synthetic analogue of the myelin protein that is believed to be involved in MS pathogenesis by having an immunomodulatory and neuroprotective effect [7; 8].

Copaxone is one of the “first-line” drugs for treating MS and is administered as an injection. Copaxone has been continuously, safely used in clinical practice in many countries for more than 20 years [9]. In terms of tolerance of Copaxone, the main challenge has been the adverse injection reactions associated with daily subcutaneous injection of a 20 mg/mL dose of the drug [9]. To address this, a new pharmaceutical form of the drug was developed – Copaxone 40 in a 40 mg/mL dosage for subcutaneous injection three times a week. International randomized studies have established that GA is clinically effective and well tolerated at a dosage regimen of 40 mg/mL three times a week (Copaxone 40) [8; 10; 11]. When Copaxone 40 was administered, the frequency of adverse injection reactions (erythema, hives, swelling, pain, or redness and irritation at the injection site) dropped 50% compared to when Copaxone 20 was used. [7; 10; 11; 13]. Use of the new form of the drug eliminated 209 injections per year [per patient], which not only significantly reduced the number of adverse reactions, but also had a favorable effect on the compliance rate and on patient satisfaction with treatment [7; 11].

Given the various pharmaceutical forms of GA that exist and the healthcare system's budget limitations, a pharmacoeconomic analysis must be performed to make a scientifically justified decision in selecting a particular drug.

The goal of this analysis was to determine, from a pharmacoeconomic perspective, the advantages that the drug Copaxone-40 used in the treatment of MS patients has over the drug Copaxone-20. To achieve the stated goal, the following tasks were performed in succession:

1. Defined the contemporary approaches to treating multiple sclerosis patients.
2. Searched the literature for the results of randomized clinical studies of the effectiveness of various MS treatment methods.
3. Tracked down earlier pharmacoeconomic research on the drugs used to treat MS.
4. Calculated the cost of MS therapy using Copaxone-20 versus Copaxone-40.

5. Performed cost minimization and budget impact analyses for the drugs being compared.

Compared alternatives and information sources

Copaxone 20 and Copaxone 40 were the alternatives being compared. It must be noted that, in analyzing the literature, it was discovered that during the period 2007 – 2013 there were reports in various countries, including the RF, of the development of new glatiramide-class drugs – the Copaxone “generics” [8]. In April 2016 two glatiramer acetate generics were registered in the Russian Federation. At the time this study was performed, no direct comparison studies of the clinical effectiveness of Copaxone versus its generic copies had been uncovered. It is important to stress that the existing Copaxone manufacturing process has a number of stringent conditions. Therefore, even slight changes at any stage of manufacturing may result in producing a finished product which has pharmacological properties that differ from those of the original and, accordingly, performs differently in terms of clinical effectiveness and tolerance, likely prompting a comprehensive program of clinical studies of this new drug to need to be performed [8].

Bearing in mind the data from clinical studies (CS) [10; 11], and the package insert recommendations [12], we examined a 365-day time horizon for using these medications and established the following dosage regimen: The 20 mg/mL Copaxone dosage was administered once a day, while the 40 mg/mL Copaxone dosage was administered subcutaneously three times a week.

based on both direct and indirect comparisons [7; 13]. The primary difference between the two drugs lies in the frequency of adverse injection reactions occurring in association with their use [7; 10; 11]. There are traditionally two types of [bilingual text:] injection-related adverse events (IRAEs). The first type includes general reactions that develop immediately after the injection, such as: shortness of breath, rapid heartbeat, headache, etc. And the second type includes [bilingual text:] injection site reactions (ISRs), such as: itchiness, pain, redness at the injection site, etc. [7; 11]. According to these studies’ findings, when glatiramer acetate is injected, injection site reactions (ISRs) are the most common to occur [7; 11]. However, the rate of adverse reactions of either type was significantly lower in patients taking Copaxone 40 [11], which is attributable primarily to its different dosage regimen. It must be noted that of the six studies we found, only in two of the studies [10; 11] were Copaxone 20 and Copaxone 40 directly compared; in all of the other studies the drug was compared to a placebo. To perform the pharmacoeconomic assessment, we chose the GLACIER study, since this work contains the most complete information on the nature and frequency of occurrence of adverse injection site reactions [11].

In performing the PE [pharmacoeconomic] analysis, the cost minimization method was used since this is the type of analysis employed in a comparison study of different forms or different application conditions of a particular drug or particular medical technology among several having comparable efficacy. [15]:

Figure 1. Weekly medication dosage regimen for the two forms of glatiramer acetate

	MO	TU	WE	TH	FR	SA	SU
Copaxone 20 mg/mL							
Copaxone 40 mg/mL							

Target population: patients over 18 years of age whose MS is exacerbated more than once in 12 months or more than twice in 24 months, and who scored between 0 and 5.5 on the EDSS (Expanded Disability Status Scale).

Searching the literature on randomized CSs in the following specialized libraries and databases (DBs) produced the sources of information on the drugs’ effectiveness: Pubmed, Medlink and ScienceOpen, and the online scientific library eLIBRARY.RU.

The following were used as sources of cost information: CMIF [Compulsory Medical Insurance Fund] rates charged for providing medical care in Moscow, standards of inpatient and outpatient care, and registered drug prices for Moscow for those drugs on the VEM [vital and essential medicines] list, and data from retail pharmacy chains (www.aptechka.ru as of 14-Sep-2015) on the cost of drugs not on the VEM list. The cost of Copaxone 20 mg/mL and 40 mg/mL was calculated based on auction prices [23].

Selection and justification of the study methods

In light of the fact that the 40 mg/mL pharmaceutical form of Copaxone appeared on the pharmaceutical market only very recently, the search for CS findings on the efficacy and safety of Copaxone–40 uncovered only a small number of works [7; 8; 10; 11; 13; 14]. All the clinical studies performed on Copaxone 40 indicate that its efficacy is comparable to that of Copaxone 20,

Cost analysis

A cost analysis was performed based on an estimation of the direct costs, specifically: the cost of the primary pharmacotherapy, of subsidies for treating MS recurrences and adverse reactions to injecting glatiramer acetate, and of providing outpatient care, as well as data on the duration of treatment of patients in the treatment groups being compared (Figure 3).

The first step was to estimate the costs of pharmacotherapy using Copaxone 20 versus Copaxone 40. All the estimates were made factoring in the dosage regimen described above, with the drug package cost given in auction prices (Table 1). The cost of administering the drug was not taken into account, because the drugs are manufactured in the form of prefilled syringes, which allows the patient to perform the injections themselves.

Despite the differences in the package cost, the cost per 1 mg is the same for the two alternatives being compared, at RUB 38.59.

At the time this study was being conducted, in effect in the Russian Federation was Russian Ministry of Health Order No. 1542n dated 24-Dec-2012 “On Approval of a Primary Healthcare Standard for Multiple Sclerosis in Remission” [16], as well as MoH [Ministry of Health] of Russia Order No.

Table 1. Pharmaceutical Form and Dosage Regimen

Dosage regimen		Package cost	Cost of a single dose	Cost for 1 month	Cost per 1 mg
Pharmaceutical form	Injections per week				
Copaxone 20 mg/mL					
Prefilled syringes, qty. 28	7	RUB 21,611	RUB 772	RUB 23,154	RUB 38.59
Copaxone 40 mg/mL					
Prefilled syringes, qty. 12	3	RUB 18,523	RUB 1,544	RUB 19,846	RUB 38.59



1534n dated 24-Dec-2012 "On Approval of a Primary Healthcare Standard for Multiple Sclerosis (Diagnosis)" [17] In accordance with regulatory documents, data from the lists of MS diagnosis and treatment services were used to calculate the cost of outpatient care, disregarding the 365 days of outpatient pharmacotherapy for patients. The cost of treatment came to RUB 48,203, both for Copaxone-20 and Copaxone-40.

Compensation for adverse reactions was calculated based on the frequency of their occurrence, which is described in work [11]. Data on the frequency of occurrence of injection-related reactions (IRAEs and ISRs) were used, which are presented in the figure below (Figure 2):

$$CMA = DC1 - DC2 = \text{RUB } 386,683 - \text{RUB } 323,459 = \text{RUB } 63,224 \quad (1)$$

where CMA [cost minimization analysis] is the cost difference, DC1 is the direct costs associated with the use of Copaxone-20, DC2 is the direct costs associated with the use of Copaxone-40,

The analysis revealed how costs change when a multiple sclerosis patient is switched from MS therapy using Copaxone 20 to Copaxone 40. An amount of RUB 63,224 was arrived at as the total additional costs incurred per MS patient using 20 mg/mL of GA daily. (Figure 4). This is because the frequency

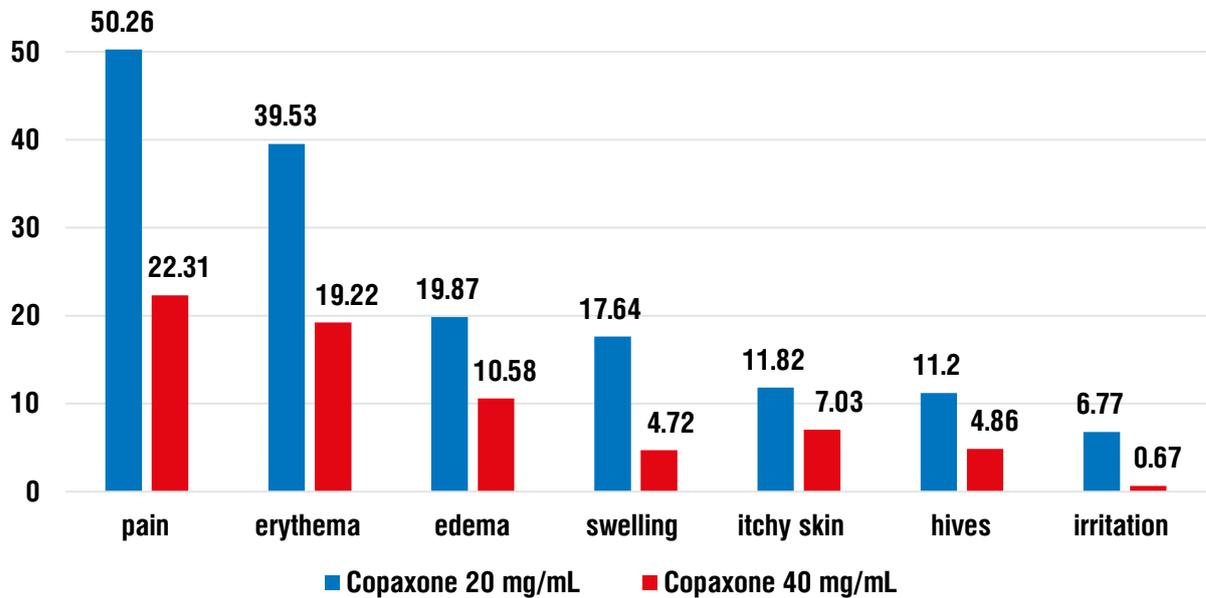


Figure 2. Most common injection site reactions (ISRs) per patient per year

Thus, the direct costs totaled: RUB 323,460 for MS treatment using a 40 mg/mL dosage of Copaxone, and RUB 386,683 for MS treatment using a 20 mg/mL dosage of Copaxone (Figure 3).

of occurrence of injection reactions when using Copaxone 20 is more than twice that which occurs when Copaxone 40 is prescribed (Figure 2). The

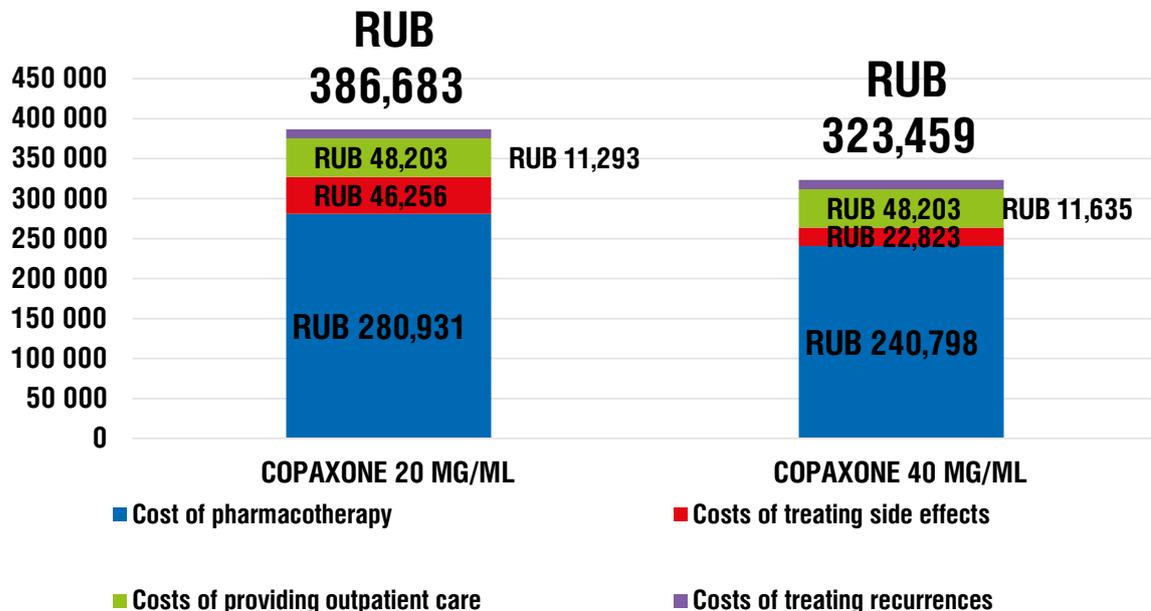


Figure 3. Cost structure for treating multiple sclerosis with glatiramer acetate

Cost minimization analysis

Because the clinical effectiveness of Copaxone 20 and Copaxone 40 is comparable, the next step of the pharmacoeconomic study was to perform a cost minimization analysis. The cost difference was obtained using the formula:

savings are quite substantial on even a per-patient basis, and become even more tangible if one extrapolates them to a large number of patients.

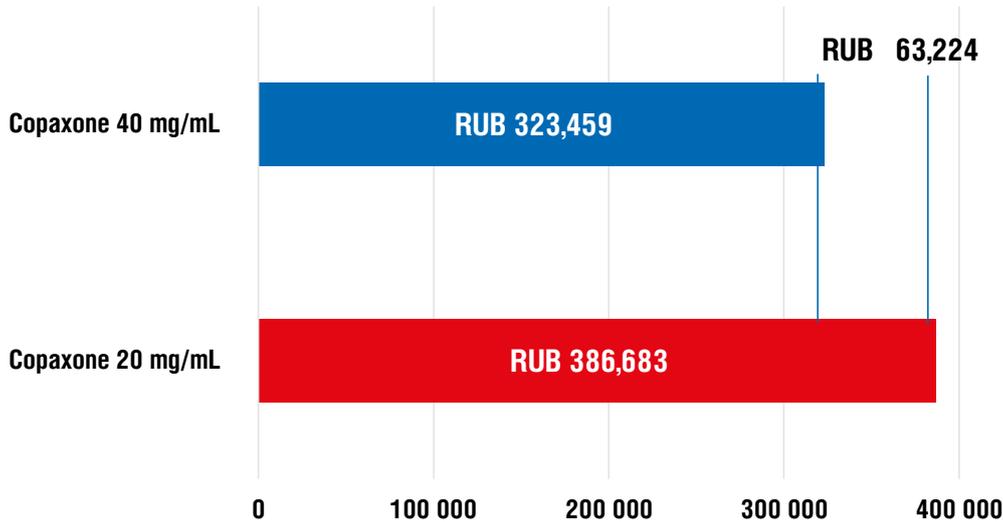


Figure 4. Results of the cost minimization analysis

Budget impact analysis

Next, on the basis of the completed cost minimization analysis, a budget impact analysis was performed to assess the economic impact on the healthcare system budget. This analysis took into consideration data on the patients' duration of treatment (365 days), the number of patients in the Russian Federation who would be taking Copaxone 20 mg/mL daily (12,850 individuals), and the auction prices for glatiramer acetate drugs. Using the auction prices made it possible to correlate budget funds earmarked for MS treatment with the calculation results obtained. This calculation makes it possible to assess the budget impact based on a change in the ratio of the alternatives being examined between the current situation and the simulated situation. In making this comparison, the hypothetical situation of switching all patients using Copaxone-20 as their pharmacotherapy to Copaxone-40 was considered (Table 2).

The cost difference was obtained using the formula:

$$BIA = Cost_1 - Cost_2 = RUB\ 4,968,878,964 - RUB\ 4,156,452,571 = RUB\ 812,426,393 \quad (2)$$

where $Cost_1$ is the total cost, in roubles, of MS treatment with all patients using Copaxone-20 (the current option);

$Cost_2$ is the total cost, in roubles, of MS treatment with all patients using Copaxone-40 (the simulated option);

BIA (Budget Impact Analysis) is the result of analyzing the impact on the budget, in roubles. [18; 19].

It was found that prescribing Copaxone 40 mg/mL three times a week for one year to 12,850 patients produces a budget savings of RUB 812,426,393 compared to using Copaxone 20 mg/mL daily for the same period of time (Fig.

5), by reducing the cost of treating the adverse reactions. These savings are due to the 209 fewer injections per patient per year that would be achieved by prescribing Copaxone 40, and consequently, the lower number of injection reactions.

Table 3. Budget Impact Analysis

Description	Number of patients (current option)	Number of patients (simulated option)
Copaxone 20 mg/mL	100%	0%
Copaxone 40 mg/mL	0%	100%
Total costs	RUB 4,968,878,964	RUB 4,156,452,571

It should be noted that a decrease in the number of injections also has an effect on a patient's therapy compliance rate. This is why, according to data from observations performed in actual clinical practice in Europe and the USA, patients demonstrated a higher compliance rate to Copaxone 40 not just when compared to Copaxone 20, but when compared to MS oral treatment drugs as well [21,22].

Discussion

A review of CS data has confirmed the comparable clinical effectiveness for the main indicator – a decrease in the number of MS recurrences per year – associated with taking Copaxone in 20 mg/mL and 40 mg/mL dosages. Cost minimization and budget impact methods were used to perform a pharmacoeconomic analysis. Using BIA, it was established that there is a budgetary savings attributable to the lower frequency of injections, and thus the lower number of adverse reactions.

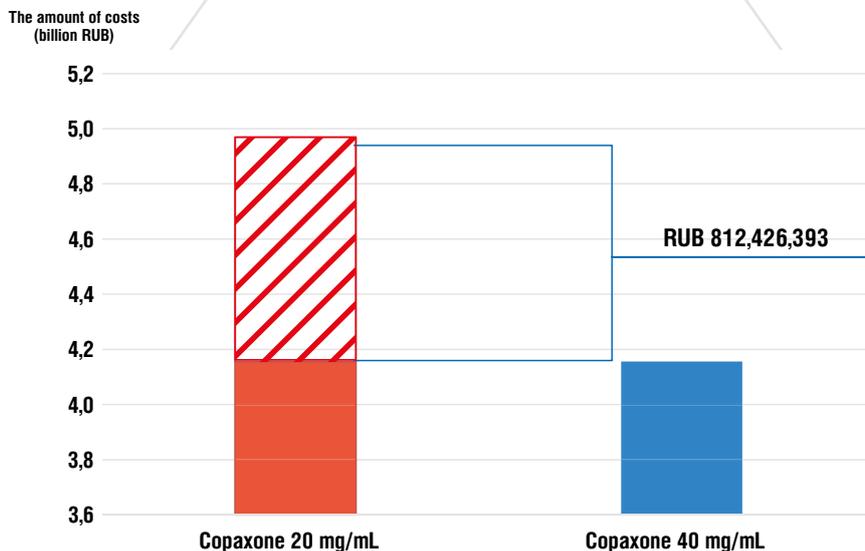


Figure 6. Results of the budget impact analysis



Conclusion

Therefore, in the course of the pharmacoeconomic analysis that was performed regarding the use of Copaxone 20 versus Copaxone 40 in the treatment of multiple sclerosis, it was established that:

1. Based on the results of the cost minimization analysis, Copaxone–40 therapy is superior to Copaxone–20 therapy and enables total direct treatment costs per multiple sclerosis patient to be reduced by more than 60,000 roubles.
2. The completed budget impact analysis revealed that if 12,850 patients in the RF were to use Copaxone 40 mg/mL therapy three times a week instead of Copaxone 20 mg/mL daily, a budgetary savings of 812 million roubles would be achieved.

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