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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
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PHARMACOECONOMIC EVALUATION OF TARGETED THERAPY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Kulikov A.Yu.[1], Komarov I.A.[1], Pochuprina A.A.[2]

[1]Laboratory of pharmacoeconomic studies of the Pharmacy Research Institute, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation

[2] FSBI «Scientific Center of Medical Expertise» Ministry of Health, Russia

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which, in the cases of high activity, results in extensive damage to various tissues and organs, as well as promotes early patient disability. Most drugs used for the treatment of SLE are currently prescribed off-label, since this specific indication is not reflected in their prescribing information. At the same time, the advent of belimumab (Benlysta®), an innovative biological product for the treatment of SLE, which represents the most severe connective tissue disorder, provided patients with an access to a highly effective targeted therapy, which specifically impacts one of the main mechanisms of the disease. The innovative and proprietary product, Belimumab, has a relatively high cost, which, as the healthcare budget is restricted, requires that a pharmacoeconomic evaluation be completed of combined use of belimumab with standard of care (SoC) versus SoC alone. The present study showed that the use of belimumab combined with SoC in patients with SLE was, clearly, associated with additional costs compared to SoC alone. However, given low incidence of the condition, the overall increase in costs is unlikely to be significant. On the other hand, it was noted that the high belimumab efficacy resulted in lower direct costs of treating the SLE (cardiovascular, cutaneous, and pulmonary) complications, as well as the costs of hospital care. A comparative analysis has demonstrated that the annual cost of treatment with belimumab was similar to the cost of other genetically engineered biological products, which have already been included into the List of Vital and Essential Drugs used for rheumatic diseases, particularly rheumatoid arthritis. In this view, the use of belimumab, which represents the only targeted drug for SLE, could be considered during the review of policy for subsidised drug provision to patients with this condition.

Key words*: systemic lupus erythematosus, pharmacoeconomic evaluation, efficacy analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, discounting, autoimmune disease, belimumab, standard therapy.*

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease caused by over-production of autoantibodies to nuclear antigens, which leads to immuno-inflammatory damage to tissues and organs [6,10,16,21]. SLE occurs most often in women of childbearing age, incidence of SLE in men is 8-15 times less than it is in women [21]. According to pooled results from epidemiological trials conducted in Europe and the United States in 1950-2006, the average prevalence of SLE was about 50 per 100,000 population [1]. In Russia, according to epidemiological studies conducted in Yaroslavl and Kursk, it was shown that the prevalence of SLE in these regions is about 9 per 100,000 population which is much less than in Europe [18]. Currently, an increase in SLE incidence is being recorded, which is thought to be associated with improvement in rheumatic diseases detection [5].

Clinical manifestations in patients with SLE can range from minor skin and joint lesions to severe complications associated with renal, gastrointestinal cardiovascular and central nervous damage [1], which, consequently, affects the cost of treatment. The need for continuous medical therapy and expensive laboratory techniques and equipment for assessing patient condition render SLE a high-cost disease. As such, according to the results of cost analysis conducted in the United States, the annual costs per patient with confirmed SLE reached approximately €10,500 in 2012, and further increased by 2.5-fold if the patient had lupus nephritis [22]. It can, therefore, be concluded that costs can vary significantly depending on activity and manifestations of the disease. At the same time, SLE increases not only the direct medical costs, but also indirect costs, due to early and persistent disability, which is recorded more than in 50% of patients with this condition [3].

Medical treatment of SLE includes the variety of products, many of which are prescribed off-label [1]. The launch of belimumab (Benlysta®) started the new era in the treatment of patients with SLE. Belimumab is an innovative targeted genetically engineered biological medicinal product (GEBP), which became the first drug specifically approved for the treatment of patients with SLE by the Food and Drug Administration (FDA) in the last 50 years [17]. Belimumab is recommended for patients with SLE, characterised by high immunological and clinical activity, without clinical manifestations of active lupus nephritis and central nervous system damage [24]. Belimumab differs from other products traditionally used for SLE (corticosteroids, aminocholine drugs and cytostatic agents), because of its distinct mechanism of action which affects one of the main pathways of SLE pathogenesis. Specifically, belimumab binds a B-lymphocyte stimulator (BLyS), which subsequently to decreases differentiation and resistance to apoptosis of B-lymphocytes [26].

The availability of belimumab for treatment of SLE in the times of budget constraints necessitated a pharmacoeconomic assessment of its use for the Russian healthcare system. Therefore, the aim of this study was to perform pharmacoeconomic evaluation of combined use of belimumab and standard of care (SoC) versus SoC alone in patients with SLE.

Materials and methods

The study population was comprised of the patients fulfilling the following criteria: adults with confirmed diagnosis of SLE according to the American College of Rheumatologists (ACR) criteria; high immunological activity; current therapy with SoC; no evidence of renal or central nervous system involvement in the pathological immuno-inflammatory process.

The analytical decision-making model was created as a part of pharmacoeconomic assessment in this model we used the following methods of analysis:

- efficacy analysis;
- cost analysis;
- cost-effectiveness analysis;
- budget impact analysis.

At the first step of pharmacoeconomic analysis, the efficacy analysis, based upon the retrieval of data to identify applicable criteria for efficacy assessment, was performed. The search was performed in eLIBRARY, Medline and Pubmed databases using the following keywords: “системная

Kulikov A. Yu tel.: +7(968) 879-88-02, e-mail: 7677041@mail.ru

красная волчанка [sistemnaya krasnaya volchanka]", "systemic lupus erythematosus", "анализ эффективности" [analiz effectivnosti], "efficacy analysis", "белимумаб" [belimumab], "belimumab", "клиническое исследование" [klinicheskoye issledovanie], «clinical trial». The search identified results of two phase III randomised placebo-controlled clinical trials of the efficacy and safety of belimumab in patients with SLE (BLISS-52 and BLISS-52) because these data are the most convincing and reliable information on the effectiveness and safety [27].

According to Food and Drug Administration (FDA), the one of most important criterion of effectiveness is the rate at the same time taking into account the clinical manifestations of the disease, the values of laboratory parameters, changes in disease activity during treatment, and the parameters of the general health of the patient [12]. An example of such a parameter can serve American College of Rheumatology criteria (ACR) 20/30/50/70, that were used to conduct pharmacoeconomic studies in the «cost-effectiveness» analysis [2,7,14].

The main criterion for assessing the efficacy of therapy in patients with SLE was Systemic Lupus Erythematosus (SLE) Responder Index (SRI). SRI is a validated index, which integrates the following assessment parameters: reduction of SLE activity index SELENA SLEDAI (Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index) by four or more points; lack of inflammatory involvement of new organs and systems, calculated according to the BILAG index (British Isles Lupus Assessment Group); and absence of deterioration of patient's general condition according to physician's assessment based on PGA (Physician's Global Assessment) scale, by more than 0.3 points [1]. Therefore, SRI allowed to simultaneously consider the clinical manifestations, laboratory markers, activity of disease, extent of involvement of various organs and systems into the inflammatory process, as well as evaluate the overall patient's condition. And that's why SRI was deemed the most appropriate efficacy criterion for pharmacoeconomic evaluation.

At the second step, a cost analysis was carried out to calculate the direct medical costs per patient. According to the results from clinical trials of BLISS-52 and BLISS-76, an average patient weight was set at 60 kg.

The following structure of medical costs associated with SLE treatment was defined:

- costs of belimumab therapy;
- costs of SoC;
- costs of outpatient and inpatient treatment;
- costs of adverse reaction management;
- costs of SLE complications treatment.

Calculation of costs associated with medical therapy with belimumab was carried out in accordance with the approved prescribing information [24]. To determine the costs of belimumab treatment, a planned-for-registration maximum selling price, including VAT, was used. Thus, the price of 1 vial of belimumab (Benlysta®) with 120 mg reached 8,250 roubles, and containing 400 mg with 27,500 roubles.

To calculate the cost of SoC, the maximum selling prices, including VAT, were used, since all SoC drugs (prednisone, azathioprine, cyclosporine, mycophenolate mofetil, hydroxychloroquine and methotrexate) had already been included into the list of List of Vital and Essential Drugs [23]. It should be noted that data regarding the SoC and proportions of patients receiving relevant drugs were taken from a clinical trial report. According to data from clinical trials, standard therapy did not include cyclophosphamide and rituximab. Therefore, these drugs were not included into further evaluation. The dosage and frequency of SoC administration was calculated based upon the approved prescribing information for relevant drugs and recommendation of the treatment SLE. Also, it should be noted that for costs calculation, data regarding decrease in oral corticosteroid dose to < 7.5 mg daily in both groups at Week 40 of the trial, were taken into consideration. In the combined treatment group (belimumab + SoC) a decrease in corticosteroid usage was recorded in 17.9% of patients as opposed to 12.3% in the SoC-only group [19].

The costs of outpatient and inpatient treatment of SLE patients were calculated in accordance with the Order of the Russian Ministry of Health from 07.11.2012 N 613n "Regarding the approval of the standard of specialist medical care for Systemic Lupus Erythematosus» and the Order of the Russian Ministry of Health from 07.11.2012 N 613n "Regarding the approval of the standard of specialist medical care for Systemic Lupus Erythematosus", and included the costs of diagnosis, treatment and medical therapy. To determine the costs of medical services, rates of the Moscow branch of the Federal fund of Mandatory Medical Insurance were used. The rate of severe relapses, registered in clinical trials, was assessed as the frequency of hospital admissions. Thus according to the report data on the clinical trial for treatment group (belimumab+SoC) the incidence of hospitalization was in 13.8% of patients, while in the treatment group only SoC - 23%.

To determine the costs associated with management of adverse events reported during the use of compared therapies, data regarding the rate of adverse events in the treatment group obtained from the BLISS-52 and BLISS-76 clinical trials, were used [19,20]. To calculate the costs associated with adverse events and SLE complications, the choice for necessary therapy and medical services required for their management was based upon the approved standards of medical care and existing guidelines.

Analysing cost-efficiency is one of the major steps in pharmacoeconomic evaluation [11]. This method of analysis allows to compare alternative treatment methods, while taking into account the cost-effectiveness of treatment by producing cost-efficiency ratios (CER) for each type of therapy. The rate of response to treatment according to the SRI scale at Week 52 of observation in two analysed groups was chosen as a criterion for assessment of therapy efficacy. To assess the costs per efficacy unit, total costs were also calculated for the entire treatment period during which the efficacy assessment was performed (52 weeks). Therefore, CER was calculated according to the following Equation 1:

$$CER=(Cost\ 52\ wks)/(\%\ SRI\ 52\ wks) \quad (1)$$

CER - cost-efficiency ratio;

Cost 52 wks - costs recorded during 52 weeks of treatment, roubles;

% SRI 52 wks - the proportion of responders to therapy according to SRI on Week 52 of treatment,%.

The study also included a budget impact analysis, which represents another important step in pharmacoeconomic evaluation [8]. This method was used to determine the extent of impact of newly introduced medical technology. This study took into account a 7-year time period, because trials of belimumab efficacy and safety in longer-term users were lacking [23]. The discount rate was set at a level of 3.5% that recommended by NICE for chosen time horizon [28].

Results

Efficacy analysis

Comparative analysis of the results of belimumab clinical trials (BLISS-52 and BLISS-76) using the selected criterion revealed that the most statistically significant results were obtained in the BLISS-52 trial. In this trial, belimumab used in conjunction with SoC demonstrated greater efficacy versus SoC only - 57.6% vs 43.6% (BLISS-52), respectively [9,13].

Cost analysis

Cost for the first year of treatment was calculated on a per-patient basis. The outcomes of cost analysis are presented in Table 1.

Table 1. **Costs for the first year of treatment per patient**

Type of costs	Belimumab+SoC, roubles	SoC, roubles
Belimumab treatment (with administration costs)	663 018	-
SoC	20 203	22 474
Outpatient visits	61 508	62 077
In-patient visits	45 271	78 452
Treatment of adverse events	3 780	3 626
Treatment of SLE complications	260 449	263 051
Total:	1 054 229	429 679

As demonstrated in Table 1, the cost of medical therapy with belimumab, which took into account the cost of required number of intravenous infusions per patient during the first year (52 weeks) of treatment, reached 663,018 roubles. It is important to note that the first year of belimumab therapy involves the administration of loading dose during the first month of treatment. The costs of belimumab treatment during the second year will, therefore, be reduced, reaching the amount of 574,825 roubles.

The cost of SoC for belimumab group was 20,203 roubles, compared to 22,274 roubles for SoC-only group (Table 1). The difference in costs was associated with different frequencies of SoC prescription in two groups.

The cost of in-patient treatment in the group receiving belimumab in conjunction with SoC was 45,271 roubles versus 78,452 roubles in SoC-only group (Table 1). Costs of adverse event management were 3,780 and 3,626 roubles, respectively. The highest costs associated with the management of observed adverse events were related to the treatment of influenza, headaches and arthralgia (Figure 1).

Treatment of complications associated with SLE activity cost 260,449 roubles in the group receiving belimumab in conjunction with SoC, and 263,051 roubles in SoC-only group (Figure 2).

Cumulative costs during the first year of treatment reached 429,679 roubles in SoC-only group, and 1,054,229 roubles in the group receiving belimumab in conjunction with SoC.

Cost-effectiveness analysis

When the selected SRI criterion was used, the cost-effectiveness coefficient in belimumab treatment group was 1,830,259 roubles, compared to 985,502 roubles in SoC-only group. Therefore, the cost required to achieve the chosen efficacy unit in belimumab and SoC group was higher than in SoC-only group.

Budget impact analysis

Outcomes of budget impact analysis based on the calculation of 7-year treatment costs per patient and discount rate of 3.5% are presented in Table 2.

Table 2. **Outcomes of budget impact analysis.**

Type of costs	Belimumab + SoC, roubles	SoC, roubles
Belimumab treatment (with administration costs)	3 713 275	-
SoC	93 863	105 884
Outpatient visits	387 910	391 480
In-patient visits	285 546	494 749
Treatment of adverse events	40 715	34 081
Treatment of SLE complications	1 642 498	1 658 907
Total:	6 163 806	2 685 101

As evidenced by data presented in Table 2, the use of belimumab is associated with a spending of budget funds. The difference in budget funds spending per patient during 5 years of treatment with a discount rate of 3.5% was 3,478,704 roubles. At the same time, reduction of direct costs with belimumab use reached 241,204 roubles during 7 years. This outcome was, most likely, caused by reduction in activity of the disease, which subsequently reduced the risk of SLE complications, particularly cardiovascular, pulmonary, renal and skin complications, and the number of days spent in hospital per year.

To assess the impact of newly introduced therapy for SLE, an additional analysis of scenarios was carried out. Inclusion of additional scenario analysis in the model shows the possible outcomes arising from the use of medical technology that should also be considered for a more complete assessment. In the model were inserted two scenarios: Scenario-1 is the calculation of cost per patient under treatment belimumab in combination with SoC with the assumption that the high efficiency of belimumab in reducing the activity of the immunological process, thus reducing the risk of developing lupus nephritis, the basis of which was the results of clinical trials of belimumab where 3.97% of patients of 1 684 people from the research, it was found renal involvement in the pathological process [11]; Scenario 2 - is the calculation of the average cost per patient with the development of lupus nephritis undergoing treatment ST. Scenario 2 includes data clinical practice, where in 50% of cases of SLE there is a severe kidney damages as lupus nephritis, and in 60% of those observed lupus nephritis class IV-V [11, 25]. The results obtained in the group of Scenario 1 and Scenario 2 are shown in Table 3.

Table 3. **Budget impact analysis using Scenario 1 and Scenario 2**

Type of costs	Scenario-1, roubles	Scenario-2, roubles
Belimumab treatment (with administration costs)	3 713 275	-
SoC	93 863	105 884
Outpatient visits	387 910	391 480
In-patient visits	285 546	494 745
Treatment of adverse events	40 715	34 081
Treatment of SLE complications	1 642 498	2 226 687
Total:	6 163 806	2 252 881

As specified in Table 3, Scenario 1 requires the use of additional funds. However, when compared with the population of patients who could develop lupus nephritis (Scenario 2), a reduction of direct costs over 7 years of therapy by 808,983 roubles can be achieved.

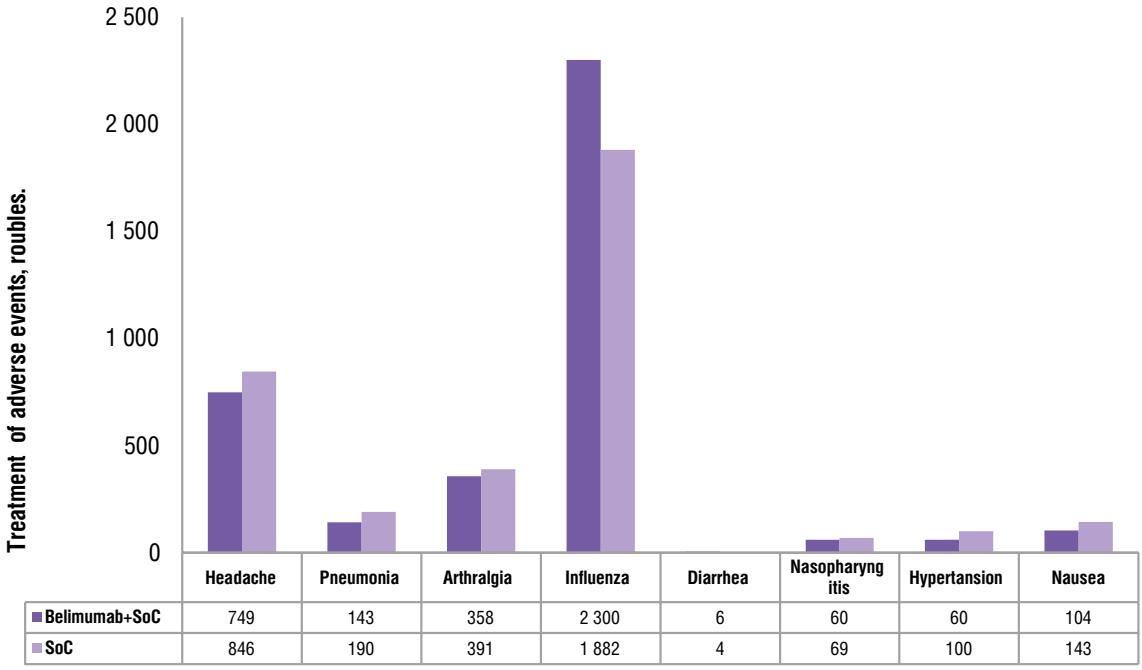
In this study it was used basic methods of pharmacoeconomic analysis necessary for the formation of the evidence base for inclusion into List of Vital and Essential Drugs. However, in the case of innovative treatment approach that is both more effectiveness and at the same time more expensive, special attention deserves the comparison of the cost of treatment required with the cost of other treatments that have been approved for preferential support.

It is also worth noting that the annual cost of belimumab treatment (excluding the costs of drug administration) per patient with a fixed weight of 60 kg is comparable to the cost of other GEBPs used for the treatment of rheumatic diseases, particularly rheumatoid arthritis (Table 4).

Table 4. **Cost comparison for belimumab and other GEBP therapy**

№	INN	TN	Method of administration	Cost of the treatment within 1 year, roublesO	List if Vital and Essential Drug
1.	Adalimumab	Humira®	Subcutaneous	975 071	Included
2.	Tocilizumab	Actemra®	Intravenous	885 397	Included
3.	Certolizumab pegol	Cimzia®	Subcutaneous	856 923	Included
4.	Infliximab	Remikad®	Intravenous	845 638	Included
5.	Abatacept	Orencia®	Subcutaneous	799 438	Included
6.	Belimumab	Benlysta®	Intravenous	663 018	Not included
7.	Etanercept	Enbrel®	Subcutaneous	620 084	Included
8.	Abatacept	Orencia®	Intravenous	459 644	Included

As evidenced by data presented in Table 4, the use of belimumab results in lower cost of medical therapy compared to adalimumab, tocilizumab, certolizumab pegol and infliximab. These products have already been included into the List of Vital and Essential Drugs for the treatment of rheumatoid arthritis in patients with insufficient response to methotrexate.



	Headache	Pneumonia	Arthralgia	Influenza	Diarrhea	Nasopharyngitis	Hypertansion	Nausea
Belimumab+SoC	749	143	358	2 300	6	60	60	104
SoC	846	190	391	1 882	4	69	100	143

Figure 1. Costs of adverse event management, roubles

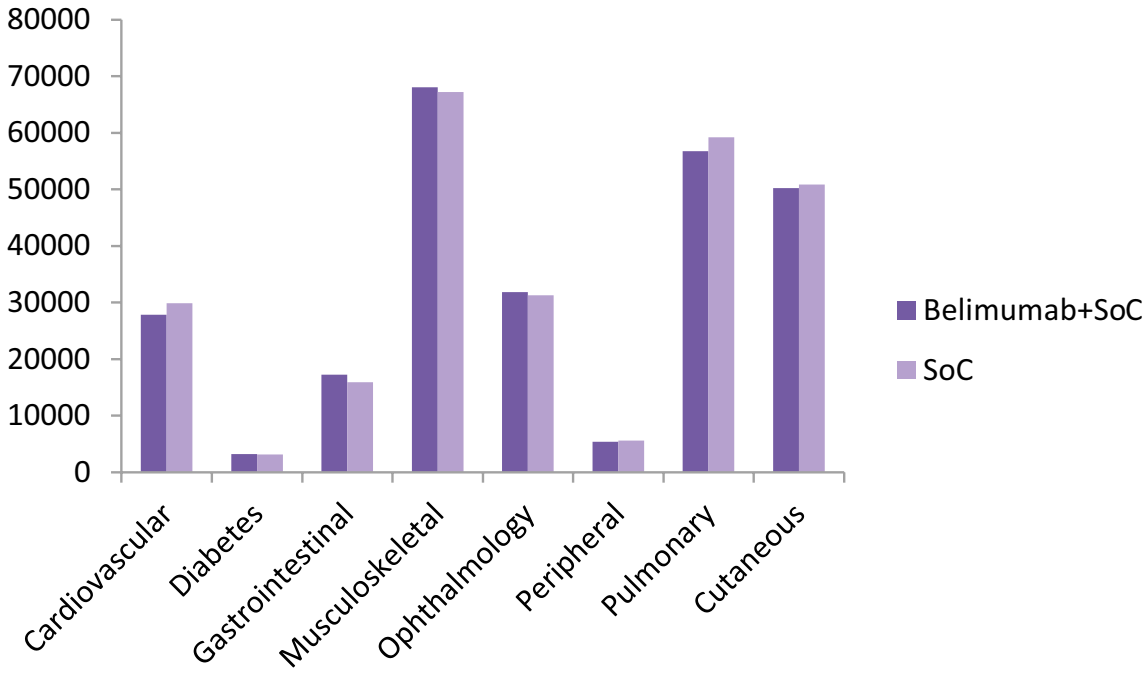


Figure 2. Costs of SLE complications treatment during the first year of therapy

Conclusions

Analysis of efficacy allowed us to conclude that therapy with belimumab represents a superior treatment option in comparison with SoC from the SRI perspective. The results of cost analysis allowed us to compare cost-effectiveness ratios. This comparison demonstrated that the costs per efficacy unit were higher in the group of belimumab in conjunction with SoC compared to SoC only. Analysis of impact upon budget, which was performed using the calculated difference of budget funds required during a 7-year period, suggested that switching to combined therapy with belimumab and SoC, compared to SoC only, leads to spending of larger amounts of budget funds. At the same time, a reduction in the direct costs of complications treatment (cardiovascular, pulmonary and skin), and hospital admission costs, was observed. This reduction was associated with the high efficacy of belimumab against disease activity. It was also shown that the cost of belimumab treatment course during the first year was comparable to that of other GEBPs, which had already been included into the List of Vital and essential Drugs for rheumatic diseases.

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