Фармакоэкономика

Результаты российских фармацевтэкономических исследований

XI Национальный конгресс с международным участием «Развитие фармацеоэкономики и фармацеоэпидемиологии в Российской Федерации» – «Фармацеоэкономика 2017»
27-28 марта 2017 г., Екатеринбург
BUDGET IMPACT ANALYSIS OF USE OF BPA ANTI-INHIBITOR COAGULANT COMPLEX (AICC) AND EPTACOG ALFA [ACTIVATED] IN THE PROPHYLAXIS OF BLEEDINGS IN INHIBITOR HEMOPHILIA PATIENTS

Serpik V.G., Yagudina R.I.

State Budgetary Educational Institution of Higher Professional Education “I.M. Sechenov First Moscow State Medical University” of the Ministry of Health of the Russian Federation, Moscow

Summary: The limited financing of the program of pharmacological support of high-cost nosologies emphasizes the importance of more effective use of the available resources. In order to improve the efficiency of use of the available resources of pharmacological support of inhibitor hemophilia patients receiving therapy in the prophylactic regimen, a budget impact analysis of prophylactic treatment by BPA anti-inhibitor coagulant complex and eptacog alfa [activated] was performed. In accordance with the instructions for use of eptacog alfa, this medicinal product is not indicated for long-term preventive treatment of bleedings, however, as eptacog alfa is used in the said regimen, it was included in the analysis. The analysis horizon period made 1 year and 75 patients were included in the analysis. The analysis shows that prophylactic anti-inhibitor coagulant complex therapy offers better control over the disease and reduces the costs. The incidence of bleedings in prophylactic anti-inhibitor coagulant complex therapy is reduced by 72.5%, while the incidence of bleedings in prophylactic treatment by eptacog alfa is reduced by 59% as compared to on demand therapy. The annual costs of prophylactic anti-inhibitor coagulant complex therapy per patient make 58.8 million rub (per adult patient) and 23.5 million rub (per pediatric patient), while the annual costs of bleeding prophylactic eptacog alfa treatment proved to be higher by 37.4% and made 94 million rub per adult patient and 37.6 million rub for pediatric patient. Transfer of all patients who respond to anti-inhibitor coagulant complex therapy and receive therapy with this medicinal product in prophylaxis regimen will save 765 million rub or 17.3% of the budget, provided that the current distribution of patients is preserved. Thus, the budget impact analysis demonstrates that the transfer of patients receiving therapy with eptacog alfa in prophylaxis regimen to AICC will improve the control over disease and save the budget funds under the 7N Program.

Key words: inhibitor hemophilia, program of pharmacological support of high-cost nosologie, prophylaxis regimen, on demand regimen, anti-inhibitor coagulant complex, eptacog alfa, pharmacoeconomics, budget impact analysis.

Introduction

The State program of pharmacological support of persons with hemophilia, mucoviscidosis, hypophyseal nanism, Gaucher’s disease, malignant neoplasms in lymphoid, blood-forming and related tissues, multicular sclerosis, as well as persons after transplantation of organs and (or) tissues (hereinafter – the Seven High-Cost Nosologies Program or the 7N Program) introduced in 2008 provides patients with severe life threatening diseases with access to the advanced high-efficient pharmacotherapy. Thus, inclusion of hemophilia, in particular, hemophilia A (congenital factor VIII deficit), hemophilia B (factor IX deficit) and Willebrand disease (Willebrand factor deficit) in the 7N Program has provided patients with access to highly needed replacement therapy by advanced medicinal products of blood coagulation factors in accordance with the standards applicable in the developed countries, which, in turn, improved the prognosis for the disease and the quality of life of patients [1,2]. The lack of necessary medication therapy in hemophilia A patients leads to their early invalidization with the longevity not exceeding 30-40 years [3]. The advanced hemophilia replacement therapy in turn improves the longevity and quality of life of hemophilia patients as compared to healthy population [1-3]. The achievements in hemophilia therapy came to life due to the government support and increased financing of the 7N Program and, in particular, its part related to the purchase of medicinal products for hemophilia therapy [1,2]. An analysis of the 7N Program in respect of hemophilia demonstrates that, as of January 2016, 6,983 hemophilia patients are registered in Russia, of which 7,756, i.e. more than 86%, are being medicated [4]. The results of the 7N Program realization in 2015 demonstrate that the hemophilia therapy costs made 11.2 billion rub, i.e. about 25% of the total program budget [5]. However, because of the unfavorable economic situation in the country, according to the draft federal budget for the year 2017 and for the planning period of the years 2018 and 2019, financing of the 7N Program is stagnated against the growth of the number of patients due to the proactive diagnosis of hemophilia [4,6] (Fig. 1).

It should be noted that the replacement coagulation factor deficiencies therapy can be complicated by development of an inhibitor, in which case the patient body produces antibodies which inactivate injected VIII or IX coagulation factors, that makes conventional replacement therapy ineffective [7,8]. The incidence of coagulation factor inhibitor in severe hemophilia patients receiving therapy with the medicinal products of factor VIII can reach up to 30% [9]. Inhibitor hemophilia patients receive therapy with bypassing agents (BPAs) [7-9].

To maintain the hemophilia therapy achievements in conditions of limited financing, the available 7N Program funds should be spent more efficient both in terms of pharmacological support of patients and search for latent managerial resources of the program. In this respect, the 7N Program analysis aimed to the improvement of management of pharmacological support of hemophilia patients and improvement of use of the available budget funds seems to be the most adequate. This could be achieved by conducting a relevant pharmacoeconomic study. A pharmacoeconomic analysis is widely used in the optimization of health services resources all over the world and, in particular, in Russia. It has a clear methodological mechanism and gives credible results. In line with the goals to be sought, we have chosen the optimization scenario of the budget impact analysis as a basic pharmacoeconomic method. This scenario affords optimum allocation of patients between the available treatment regimens to achieve maximum efficiency of therapy within the planned budget.
The purpose of the first stage of analysis was to study the product range availability and practical administration of BPA to treat inhibitor hemophilia as a part of the 7N Program. The 7N Program has always had a fixed list of medicinal products approved by the Government of the Russian Federation on an annual basis. Since 2010, in accordance with Decree of the Government of the Russian Federation No. 2053-p [10] dated 31.12.2008, the only BPA for inhibitor hemophilia therapy under international nonproprietary name (INN) eptacog alfa [activated] (hereinafter – eptacog alfa) has been included in the list of medicinal products of the 7N Program. Since then, the list has remained unchanged over next four years up until 2014, and eptacog alfa has been the only medicinal product for inhibitor hemophilia therapy available under the federal procurement program. In 2014, the Government of the Russian Federation issued Decree No. 2782-p [11] dated 30.12.2014 which contained an updated list of medicinal products, which included, among others, anti-inhibitor coagulant complex (AICC). Both of the above BPAs have been included in the analysis.

It should be noted that patients differently respond to the BPA therapy: 30% of patients have no clinical response to one or another of the BPA and should receive therapy with the alternative BPA. That means that, to make therapy effective, both of the BPA should be available.

In the Russian Federation, BPA are currently represented by two INNs and a number of relevant trade names (TNs). AICC is represented by the only TN, Feiba (Baxter AG, Austria), while eptacog alfa is represented by two TNs, NovoSeven (Novo Nordisk A/S, Denmark) and Coagil-VII (ZAO Generium, Russia).

Analysis of the product range availability of medicinal products for inhibitor hemophilia therapy under the 7N Program

Approaches to inhibitor hemophilia therapy

Pathogenetic pharmacotherapy of hemophilia, including inhibitor hemophilia, can be carried out in two basic regimens [7,8]:

- prophylaxis regimen, when the product is prescribed to a patient to prevent bleedings;
- on demand regimen, when the product is prescribed to a patient to stop bleedings.

The prophylaxis pathogenetic therapy of inhibitor patients is considered as optimal, as it insures safety of patients from spontaneous bleedings and prevents or slows down the degenerative changes in joints, organs and tissues [7].

The analysis of prescribed therapy performed as part of the prospective multi-center open-label study non-interventional observational two-year (2014-2016) study presented by Zozulya N.I. [12] et al. demonstrate significant reduction of the share of patients with more than 5 bleedings per year – almost twice from 73% to 38%, which is associated with the growth of BPA prophylaxis from 41% to 51%. The data presented by the investigators illustrate the need in availability of both BPA for possible transfer of resistant patients to the alternative product and suppose that the improvement in the course of a disease in the population and improvement of the quality of support of patients are interrelated (Fig. 2).

It should also be noted AICC is the only BPA with the officially registered long-term prophylaxis indication [13]. According to the instruction for use, eptacog alfa represented by two TNs, NovoSeven and Coagil-VII, is used to stop bleedings, and to prevent bleedings during surgical interventions. Besides, TN NovoSeven has registered short-term prophylaxis indication (3 months or less in case of 4 and more bleedings per month), while TN Coagil-VII has no prophylaxis indication [14-15].

Fig. 1. Financing of the 7N Program by year

Fig. 2. A share of patients receiving therapy in prophylaxis regimen in all patients receiving therapy with AICC and eptacog alfa and share of replacement pharmacotherapy patients who had more than 5 bleedings per year in average, %
Specifics of inhibitor hemophilia therapy in Russia

The long practice of administration of eptacog alfa as the only BPA for therapy of inhibitor hemophilia patients because of its availability under the 7N Program has led to the current situation when most of patients are continued to receive therapy with eptacog alfa in prophylaxis regimen, notwithstanding the fact that additional medicinal product with the registered long-term prophylaxis indication has been included in the Program. This is demonstrated by the data from the observational clinical register as of June 2016 published by Zozulya N.I. et al. according to which the total number of inhibitor hemophilia patients in 2016 was 219, of which 147 patients received therapy with AICC and eptacog alfa. 75 patients or 51% of all patients received therapy with BPA in prophylaxis regimen and eptacog alfa was prescribed most commonly (54 patients or 73% of all patients receiving therapy in prophylaxis regimen) [12].

The presented epidemiological evidence made a basis for our comparative pharmacoeconomic analysis of AICC and eptacog alfa long-term prophylaxis of inhibitor hemophilia patients.

Methodology and assumptions

The study horizon period makes 1 year, as the 7N Program budget is planned on the basis of orders for 1 year. In this connection and in order to reflect the practice of BPA therapy in the Russian Federation, we have assumed that eptacog alfa was used in prophylaxis regimen for 1 year without interruption.

In our analysis, the efficiency of two TNs of eptacog alfa registered in Russia was taken as equal, as they are presented by the same INN. In the cost analysis, we used the tender price of the BPAs, as the analysis was performed with relation to the 7N Program.

The budget impact analysis was based on the population data from the epidemiological study by Zozulya N.I. et al. [12].

Efficiency Analysis

In accordance with the methodology of the budget impact analysis, we have performed a comparative evaluation of the efficiency of the BPAs, determined the dosage regimen and built a relevant decision tree model [16]. As a criterion of efficiency, we have used the most relevant parameter for evaluation of inhibitor hemophilia prophylaxis, i.e. reduction of the incidence of bleedings. We have performed information search and identified two clinical studies (with the comparable design) of the efficiency of BPA AICC and eptacog alfa preventive treatment of inhibitor hemophilia patients in comparison with the on demand therapy.

The PROOF study of use of AICC in prophylaxis regimen by Antunes S.V. et al. 2014 [17] was a prospective randomized clinical study with 34 patients and with the initial incidence of bleedings of more than 1 per month [17]. The study demonstrates that the incidence of bleedings has reduced by 72.5% in case of prophylaxis with AICC in a dose of 85 U/kg every other day as compared to the on demand therapy (Table 2) [17].

The study of use of eptacog alfa in prophylaxis regimen by Konkle BA et al. 2007 [18] was a prospective randomized clinical study with 22 patients and with the initial incidence of bleedings of more than 4 per month. The study demonstrates that the incidence of bleedings has reduced by 45% and 59% in case of prophylaxis with eptacog alfa in doses of 90 and 270 µg/kg, respectively, every day, as compared to the on demand therapy [18].

Since then, the costs of bleeding prophylaxis with BPA AICC were determined in the budget impact analysis with a dose of 85 U/kg every other day. When calculating costs of prophylaxis with eptacog alfa, a dose of 270 µg/kg daily was used as the most efficient dose (Table 2).

At the same time, it should be noted that the groups of patients in the clinical studies were heterogeneous and the horizon period was different. In particular, in the study by Konkle BA et al. 2007 [18], patients received on demand therapy for 3 months, then they received prophylaxis for another 3 months and then again on demand therapy for 3 months and were observed after therapy in prophylaxis regimen. The monthly average number of bleedings before therapy made 5.3, under the assumption of possible one-year extrapolation, it makes 63.6 bleeding episodes per year. At the same time, in the study PROOF by Antunes S.V. et al. 2014 [17], the change in the number of bleeding episodes was calculated on the basis of the average number of bleedings per year, which made 28.7 bleeding episodes before therapy in prophylaxis regimen.

Because of lack of clinical studies of the efficiency of the compared BPAs in prophylaxis regimen in homogenous groups of patients, we have used the full-scale comparative FENOC study of AICC and eptacog alfa on demand therapy by Astemark J. et al 2007 [19] as a source of data on the average incidence of bleedings. According to this study, the number of bleeding episodes in inhibitor hemophilia patients made 43.9 per year, and the average doses for stopping one bleeding made 84.6 U/kg for AICC and 212.5 µg/kg for eptacog alfa. It should be noted that the outlined approach has been already used in the work by Yagudina R.I. et al. 2013 on the pharmacoeconomic evaluation of BPA in on demand therapy of inhibitor hemophilia patients [20]. Thus, the incidence of bleedings in case of therapy with the BPAs under review in prophylaxis regimen, as shown in the studies by Antunes S.V. et al. 2014 and Konkle BA et al. 2007, was extrapolated to 43.9 basic bleeding episodes per year (Table 2).

Table 2. Efficiency Analysis Results

<table>
<thead>
<tr>
<th>Prophylaxis Scheme</th>
<th>Number of Bleedings in on Demand Therapy, Bleedings per year</th>
<th>Reduction of the Incidence of Bleedings, %</th>
<th>Estimated Number of Bleedings against Prophylaxis, Bleedings per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>eptacog alfa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>270 µg/kg every day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AICC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85 U/kg every other day</td>
<td>43.9 [7]</td>
<td>59% [18]</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>72.5% [17]</td>
<td>12.1</td>
</tr>
</tbody>
</table>

In our study, we has built a decision tree on the basis of the efficiency analysis subject to the preventive therapy of bleedings in inhibitor hemophilia patients in the Russian Federation (Fig. 3).

In the above model, the average inhibitor hemophilia patient received either AICC or eptacog alfa in prophylaxis regimen. Prophylaxis with each BPA could either be effective or ineffective (against the initial status of patient in case of on demand therapy) and could be described by absence or presence of bleedings, respectively. This model considered the prophylaxis inefficiency associated with the bleedings against therapy and the prophylaxis inefficiency associated with the resistance to one of the BPAs. In the first instance, when bleedings developed because of inefficient prophylaxis, the patient received additional therapy with the relevant medicinal product in on demand regimen. The average dose necessary to stop one bleeding in case of on demand therapy made 84.6 U/kg of AICC and 212.5 µg/kg of eptacog alfa. [19]. As the BPAs under review were dosed per kg of body weight, the mean weight in the described model was taken equal to 75 kg for adult patient and 30 kg for pediatric patient. In the second case, in case of inefficiency against the resistance to the medicinal product in 30% of patients, it was assumed in the model that a patient would be transferred to the alternative medicinal product. The pharmacoeconomic analysis was performed assuming that all patients are compliant and do not miss receiving the medicinal product.

Cost Analysis

The purpose of the next stage of the study was to analyze the prices for the medicinal products purchased under the 7N Program. Information was obtained from the 2016 centralized federal tender for purchase of AICC and eptacog alfa [5]. The tender unit prices of the active substance are presented in Table 3.

Table 3. Unit price of the active substance of the BPAs under review following the results of the 2016 7N tender; VAT not included

<table>
<thead>
<tr>
<th>INN</th>
<th>Dosage</th>
<th>Tender Price per Unit of Active Substance, rub</th>
<th>Average Tender Price per Unit of Active Substance, rub</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICC (in U)</td>
<td>500</td>
<td>47.35</td>
<td>47.36</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>47.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>12.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4</td>
<td>12.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.8</td>
<td>12.10</td>
<td></td>
</tr>
</tbody>
</table>

The costs [21] of bleeding prophylaxis with each of the BPAs in one inhibitor hemophilia patient were calculated on the basis of the dosage regimen and unit price of the active substance of the BPA (Formula 1).
Cost(Proph) = w*dP*price*nP, where:
- Cost(Proph) – costs of the annual course of the pharmacotherapy in prophylaxis regimen, rub;
- wP – patient weight, kg;
- dP – single dose of the medicinal product per kg of the patient weight in prophylaxis regimen, U or µg;
- price – unit price of the active substance of the BPA, rub;
- nP – number of days of administration of the BPA per year.

In the first instance, the course costs of the annual medicinal product prophylaxis were determined and made (for AICC):
- per 1 kg of the patient weight (Fig. 4.):
  - 1 * 85 * 47.36 * 183 = 736,685 rub
  - 75 * 85 * 47.36 * 183 = 55,245,527 rub per adult patient
  - 30 * 85 * 47.36 * 183 = 22,098,211 rub per pediatric patient.

The costs of the annual eptacog alfa bleeding pharmacotherapy course in one inhibitor hemophilia patient made:
- per 1 kg of the patient weight (Fig. 4.):
  - 1 * 270 * 12.26 * 365 = 1,208,223 rub
  - 75 * 270 * 12.26 * 365 = 90,616,725 rub per adult patient
  - 30 * 270 * 12.26 * 365 = 36,246,690 rub per pediatric patient.

The next stage of the analysis included calculations of the costs of the medicinal products, used in the on demand regimen to stop bleedings because of inefficient prophylaxis in one patient per year. The following formula (2) was used for calculations:

Cost(OnDemand) = w*dd*price*b*(1-ef), where:
- Cost(OnDemand) – costs of the annual course of the pharmacotherapy in on demand regimen, rub;
- w – patient weight, kg;
- dd – course dose of the medicinal products in on demand regimen per kg of patient weight, U or µg;
- price – unit price of the active substance of the BPA, rub;
- b – number of bleedings per year in on demand regimen.
- Ef – reduction in the incidence of bleedings in case of therapy in prophylaxis regimen compared to on demand regimen.

The annual costs of AICC for stopping bleedings against prophylaxis made:
- (75 * 84.6 * 47.36 * 43.9 * (1 – 0.725)) = 3,627,394 rub per one adult patient.
- (30 * 84.6 * 47.36 * 43.9 * (1 – 0.725)) = 1,450,957 rub per one pediatric patient.

The similar annual costs in case of eptacog alfa prophylaxis made:
- (75 * 212.5 * 12.26 * 43.9 * (1 – 0.59)) = 3,416,892 rub per one adult patient.
- (30 * 212.5 * 12.26 * 43.9 * (1 – 0.59)) = 1,406,757 rub per one pediatric patient.

Accordingly, the total annual costs of AICC inhibitor hemophilia therapy in prophylaxis regimen, including costs of the medicinal product to stop bleedings, made 58,872,920 rub per one adult patient and 23,549,168 rub per one pediatric patient (Fig. 4-5).

At the same time, the costs of use of eptacog alfa in the course of the year to prevent bleedings, including costs of the medicinal product to stop bleedings, made:

Cost(Proph) = w*dP*price*nP, where:
- Cost(Proph) – costs of the annual course of the pharmacotherapy in prophylaxis regimen, rub;
- wP – patient weight, kg;
- dP – single dose of the medicinal product per kg of the patient weight in prophylaxis regimen, U or µg;
- price – unit price of the active substance of the BPA, rub;
- nP – number of days of administration of the BPA per year.
bleedings occurring against bleeding prophylaxis, made 94,133,617 rub one adult patient and 37,653,447 rub per one pediatric patient (Fig. 5-6).

The obtained data demonstrate that the costs of AICC prophylaxis of bleedings in inhibitor hemophilia patients are lower by 37.4% than those of eptacog alfa prophylaxis with the AICC prophylaxis being more efficient in terms of lower incidence of bleedings.

**ANNUAL COSTS PER ONE ADULT PATIENT**

- **Prophylaxis**
  - AICC
    - 347,394 P
  - Eptacog Alfa
    - 90,616,725 P
- **On-demand therapy to stop bleedings**
  - AICC
    - 55,245,527 P
  - Eptacog Alfa
    - 36,246,690 P

**Fig. 5.** Results of the analysis of use of AICC and eptacog alfa for prophylaxis of bleedings in one adult inhibitor hemophilia patient

**ANNUAL COSTS PER ONE PEDIATRIC PATIENT**

- **Prophylaxis**
  - AICC
    - 1,400,957 P
  - Eptacog Alfa
    - 36,246,690 P
- **On-demand therapy to stop bleedings**
  - AICC
    - 22,098,211 P
  - Eptacog Alfa
    - 36,246,690 P

**Fig. 6.** Results of cost analysis of use of AICC and eptacog alfa bleeding prophylaxis in one pediatric inhibitor hemophilia patient

**BUDGET IMPACT ANALYSIS RESULTS**

- **Eptacog alfa**
  - Budget in case of current distribution of patients (AICC - 21 patients, Eptacog Alfa - 54 patients): 865,431,931 P
  - Budget in case of simulated distribution of patients (AICC - 52 patients, Eptacog Alfa - 23 patients): 2,142,974,305 P
- **AICC**
  - Budget in case of current distribution of patients: 3,568,250,727 P
  - Budget in case of simulated distribution of patients: 1,515,551,235 P

**Fig. 7.** Budget impact analysis results

**Budget Impact Analysis**

As part of our budget impact analysis, we have calculated annual budgets for treatment of the entire target group of inhibitor hemophilia patients with the compared medicinal products. The number of patients in the target group was calculated on the basis of the pharmacoepidemiologic study by Zozulya N.V. et al. 2016, with the description of the federal register of patients, and made 75 patients [12].
The budget impact analysis demonstrates that the transfer of all patients receiving therapy with BPA of AICC in prophylaxis regimen may result in savings of approximately 765 million rub per year which is sufficient for pharmacological support of 75 hemophilia patients. (Fig. 8) as compared to the budget is case of the current distribution of patients between the BPAs. In case of AICC therapy, the estimated budget is less than the current budget for therapy in prophylaxis regimen by 17.3%. The savings of the transfer of patients from eptacog alfa to AICC prophylaxis will be sufficient for therapy of additional 12 adult or pediatric patient hemophilia patients with BPA of AICC in prophylaxis regimen per year. It should be noted that according to the observational clinical register, the two-year growth in the number of inhibitor hemophilia patients who need therapy in prophylaxis regimen made 15 patients [12]. Therefore, the savings of transfer of all patients receiving therapy in prophylaxis regimen to AICC as it was identified in the course of the budget impact analysis will be sufficient for treatment of all patients to whom prophylaxis is prescribed for the first time, in the next year.

Conclusion

The budget impact analysis of the 7N Program with regard to the pharmacological support of inhibitor hemophilia patients receiving therapy in prophylaxis regimen demonstrates advantages of AICC over eptacog alfa. First, AICC is the only BPA with the registered long-term prophylaxis indication. At the same time, AICC therapy is accompanied by less incidence of bleedings against therapy in prophylaxis regimen; in terms of the course costs per one patient per year, AICC therapy results in costs reduction by 35.2 million rub (per adult patient) and 14.1 million rub (per pediatric patient) as compared to the costs of eptacog alfa therapy. The budget impact analysis of transfer of patients from eptacog alfa to AICC in the pharmacological support of inhibitor hemophilia patients demonstrates potential savings of 765 million rub or 17.3%.

The budget impact analysis demonstrates that the transfer of the patients receiving therapy with eptacog alfa in prophylaxis regimen to AICC will be accompanied by the better control over the disease and savings of the 7N Program funds.

Bibliography

5. IMS data – reference
7. Recommended Guidelines under the Editorship of Savchenko.
8. Recommended Guidelines under the Editorship of Rumyantsev.
13. State Register of Pharmaceutical Products. Feiba. Instructions for Use
14. State Register of Pharmaceutical Products. NovoSeven. Instructions for Use
15. State Register of Pharmaceutical Products. Coagil-VII. Instructions for Use