

The government regulation of medicine provision for patients with high-cost nosologies in Russia

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ABSTRACT

This study aimed at updating important changes in the state regulation of medicine provision for high-cost nosologies in Russia. As a result, it was found that the regulatory framework for expensive nosologies has improved in the context of serious discussions among various pharmaceutical market regulators, medicine circulation entities, and nonprofit public organizations. Further federalization of the expenses for the medicine provision may be the main development direction for the segment of cost-demanding nosologies in the Russian Federation in the nearest future.

Keywords: high-cost (cost-demanding) nosologies in Russia, orphan diseases, medicine provision

Introduction

The increasing growth in science and technology has generated wide changes in terms of health services, which has resulted in the demand for retraining to maintain competencies and job skills.^[1] Medications are crucial in healthcare delivery, and when used appropriately, they can help in treating diseases, alleviate symptoms, and lessen patient suffering.^[2] In addition, the main aim of any treatment employing drugs is not only to increase the therapeutic index of the drug but also to minimize its side effects.^[3] In 2018, important changes took place in the Russian government regulation of medicine provision for people with orphan diseases.

The adopted Federal Law led to the expansion of the List of cost-demanding nosologies for five rare diseases to twelve items.

Wide discussions both in the professional community and in the Russian Parliament in the process of reviewing the draft law had preceded this event.

The key feature of the ongoing discussion is the availability of modern treatment of patients with rare diseases, depending on funding sources.

Methods

System analysis of the national legal regulation of medicine provision of patients with high-cost nosologies has been carried out including:

Identifying the problem of medicine provision of high-cost nosologies based on a high-profile discussion in early 2018 of the draft law on the federalization of expenses for additional nosologies in the industry media (Pharmaceutical Bulletin, Moscow pharmacies);

Studying the substantive components of the existing regulatory documents on the keywords "cost-demanding nosologies in Russia", "orphan diseases", "provision of medicines" (Consultant and Garant legal bases) based on the hierarchy of the national legal regulation system "federal law – bylaws";

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Implementing the comparative and actualization analyses based on the changes that have been made to the current regulatory documents during 2012 – 2018.

Logical generalization of the results:

Determining relationships in high-cost nosologies between the two regulators: Ministry of Health of Russia (medicine provision) and Ministry of Industry and Trade of Russia (development of the Russian pharmaceutical industry).

Identifying features and prospects for improving financial support mechanisms based on the study of the roadmap for the development of competition in health care, instructions from Russian President Vladimir Putin on improving the efficiency of the medicine provision system for the population in Russian Federation.

Results

The state guarantees in the form of provision of medicines to citizens with cost-demanding nosologies and sources of financial resources are stipulated by Federal law on the health protection of citizens (Articles 44, 83, 14).

The procedure for organizing the provision of people with high-demanding diseases and the list of medicines should be established by the Russian Government.

A systematic analysis of the national statutory control of the commerce in medicines made it possible to determine that the Cost-Demanding Nosology segment included rare diseases, some other diseases (multiple sclerosis, Chronic lymphocytic leukemia), as well as transplanted organ and tissue status.

Diseases with the prevalence of no more than 10 cases per 100 thousand people are rare (orphan) diseases.

The critical point is that government regulation actually defines three lists associated with rare diseases:

- The list of rare (orphan) diseases (General List, containing above 200 groups with more than 400 diseases) should be compiled by the authorized federal executive body based on the statistical data, and be posted on its official website on the Internet;^[4]
- At the beginning of 2019, the list of life-threatening and chronic progressive rare (orphan) diseases leading to a decrease in life expectancy or disability of citizens included 19 diseases (Federal Law on the Protection of Citizens' Health, Art. 44, Decree of the Russian Federation Government No. 403 dated 26.04.2012);
- The list of cost-demanding nosologies named "Seven cost-demanding nosologies" until mid-2018 now represents the extended segment "Twelve high-cost nosologies" (Federal Law No. 299-FZ dated 03.08.2018, Decree of the Government of Russia No. 1416 dated 26.11.2018).

Until mid-2018, the informal name of the "Seven cost-demanding nosologies" program included the following diseases: hemophilia, mucoviscidosis, hypopituitarism, Gaucher disease, malignant neoplasms of lymphoid, hematopoietic and related

tissues, multiple sclerosis, and transplanted organ and tissue status.

In mid-2018, the Federal Law on the Protection of Citizens' Health was amended, supplementing cost-demanding nosologies with five new diseases, namely: hemolytic-uremic syndrome, systemic-onset juvenile arthritis, and mucopolysaccharidosis of types I, II, and VI (Federal Law No. 299-FZ dated 03.08.2018). These five diseases were included in the list of life-threatening and chronic progressive rare (orphan) diseases until mid-2018. Thus, the cost-demanding nosology segment includes rare diseases, as well as such diseases as multiple sclerosis, chronic lymphocytic leukemia, and transplanted organ and tissue status. Article 14 of the Federal Law on the Protection of Citizens' Health states that the Ministry of Health of Russia is responsible for organizing the provision of persons with twelve high-cost nosologies.

The authorities of the Russian constituent entities in the field of health care is responsible for organizing the provision of citizens with medicinal products and specialized medical nutrition for the treatment of other rare (orphan) diseases leading to a decrease in a citizen's life expectancy or disability (Article 16 of the Federal Law on public health).

The order of the Government of Russia No. 2738-p dated December 10, 2018, approved the list of vital and essential medicines for 2019, as well as the resulting three lists of state regulation of medicine circulation.^[5]

Annex 3 of the Order of the Government of Russia No. 2738-p dated December 10, 2018, includes the list of medicines intended for the treatment of cost-demanding nosologies (hereinafter referred to as the list).

The list for 2019 includes medicines for seven cost-demanding nosologies:

1. Hemophilia D66-68*,
2. Mucoviscidosis E.84,
3. Hypopituitarism E23.0,
4. Gaucher Disease E75.2,
5. Malignant neoplasms of lymphoid, hematopoietic, and related tissues (group C),
6. Multiple sclerosis (Multiple sclerosis disseminated G35), and
7. Transplanted organ and tissue status (Transplanted organ and tissue status Z94).

*International Statistical Classification of Diseases and Related Health Problems, 10th Revision

The medicines in the list for patients with hemophilia refer to the ATC code "B02B Hemostatic agents" and are the blood coagulation factors (B02BD).

For 2019, the list for hemophilia includes eight items, namely:

- Anti-inhibitory coagulant complex;
- Moroctocog alfa;
- Nonacog alfa;
- Octocog alfa;
- Blood-coagulation factor VIII;
- Blood-coagulation factor IX;

- Blood-coagulation factor VIII + von Willebrand factor; and
- Eptacog alfa activated.

The medicine from the list for patients with Mucoviscidosis "Dornaza alpha" refers to the ATC code "R05 Cough and cold preparations" and is a mucolytic agent (R05CB).

For patients with hypopituitarism, the list includes Somatropin medicine referring to the ATC code "Pituitary and hypothalamic hormones and analogues".

Velaglucerase alfa and Imiglucerase are included in the list as two enzyme preparations (ATC A16AB) to treat Gaucher disease.

It should be noted that malignant neoplasms of lymphoid, hematopoietic, and related tissues include many diseases:

- Chronic myeloid leukemia (C92.1),
- Waldenstrom macroglobulinemia (C88.0),
- Erythroid myeloma (C90),
- Follicular (nodular) non-Hodgkin lymphoma (C82),
- Small cell (diffuse) non-Hodgkin's lymphoma (C83.0),
- Small cell with split nuclei (diffuse) non-Hodgkin lymphoma (C83.1),
- Large cell (diffuse) non-Hodgkin lymphoma (C83.0),
- Immunoblastic (diffuse) non-Hodgkin lymphoma (C83.4),
- Other types of diffuse non-Hodgkin lymphomas (C83.8),
- Diffuse non-Hodgkin lymphoma, unspecified (C83.9),
- Other and unspecified types of non-Hodgkin lymphoma (C85),
- Chronic lymphocytic leukemia (C91.1).

For the treatment of the above diseases according to the ATC code "L antineoplastic and immunomodulating agents", the list includes five medicines of various groups: Fludarabine "L01BB Purine Analogs", Rituximab "L01XC Monoclonal Antibodies", Imatinib "L01XE Protein Kinase Inhibitor", Bortezomib "L01XX Other Antineoplastic Medicines", and Lenalidomide "L04AX Other Immunosuppressants".

The medicines in the list for patients with multiple sclerosis refer to two ATC groups "L03 Immunostimulants" and "L04 Immunosuppressants".

Immunostimulants are represented by three interferons (L03AB: Interferon beta-1a, Interferon beta-1b, Peginterferon beta-1a) and another immunostimulant (L03AX Glatiramer acetate).

Peginterferon beta-1a has been included in the list for 2019 for the first time.

Immunosuppressants include selective Natalizumab and Teriflunomide (L04AA) items.

The provision of patients after organ and/or tissue transplantation is provided by selective Mycophenolate mofetil and Mycophenolic acid (L04AA) immunosuppressants, as well as Tacrolimus and Cyclosporin (L04AD) calcineurin inhibitors.

Thus, 27 medicines are procured using the funds from the federal budget to provide patients with seven cost-demanding nosologies.

In mid-2018, the Russian Federal Law on the Protection of Citizens' Health was amended, supplementing cost-demanding nosologies with five new diseases, namely: hemolytic-uremic syndrome, systemic-onset juvenile arthritis, and mucopolysaccharidosis types I, II, and VI (Federal Law No. 299-FZ dated 03.08.2018).

As of June 2018, the Federal Register of life-threatening and chronic progressive rare diseases included 2,130 patients with these five nosologies, of which 1,583 were children. In general, for patients with five additional diseases, it is necessary to purchase eight medicines worth RUB 10 billion per year.^[6]

For patients with hemolytic-uremic syndrome, Eculizumab needs to be procured; the cost of treating one patient per year is RUB 10.43 million.

For patients with type I mucopolysaccharidosis, Laronidase is planned to be delivered (the cost of the annual course per patient is RUB 2.14 million), for those with type II mucopolysaccharidosis – Idursulfase (the cost of the original medicine is RUB 12.25 million per person per year), and for patients with type VI mucopolysaccharidosis – Halsulfase (RUB 13.98 million per person per year).

It is important to note that the Halsulfase and Idursulfase Beta were included for the first time in the list of life-saving and essential medicines for 2019 and one should expect the inclusion of these medicines in the list of medicines for the treatment of cost-demanding nosologies for the following years.

Several medicines – Tocilizumab, Adalimumab, Canakinumab, Etanercept – are procured for patients with systemic-onset juvenile arthritis. The average cost of a course for one patient is RUB 2.21 million. The most expensive medicine is Canakinumab, the annual course of which costs RUB 7.4 million, and Tocilizumab is the least expensive one, with the annual cost per patient being RUB 223.65 thousand.

At the end of 2018, the Ministry of Health of Russia for the first time announced auctions for the purchase of medicines for five additional cost-demanding nosologies.

As part of the implementation of the Federal Law No. 299-FZ dated 03.08.2018, the auctions were announced for the following seven medicines:

- **Etanercept**, solution for subcutaneous administration, 50 mg/ml, 1 ml (initial (maximum) contract price: RUB 18,706,841.04);
- **Etanercept**, lyophilisate for preparation of solution for subcutaneous administration, 10 mg (initial (maximum) contract price: RUB 308,151.20);
- **Etanercept**, lyophilisate for preparation of solution for subcutaneous administration, 25 mg (initial (maximum) contract price: RUB 8,712,522.00);
- **Idursulfase**, concentrate for solution for infusion, 2 mg/ml, 3 ml (initial (maximum) contract price: RUB 999,955,529.43).
- **Tocilizumab**, concentrate for solution for infusion, 20 mg/ml, 10 ml (initial (maximum) contract price: RUB 324,870,522.84).

- **Tocilizumab**, concentrate for solution for infusion, 20 mg/ml, 4 ml (initial (maximum) contract price: RUB 121,184,355.60);
- **Canakinumab**, lyophilisate for preparation of solution for subcutaneous administration, 150 mg (initial (maximum) contract price: RUB 704,610,081.24);
- **Ecilizumab**, concentrate for solution for infusion, 10 mg/ml, 30 ml (initial (maximum) contract price: RUB 999,715,554.00);
- **Adalimumab**, solution for subcutaneous administration, 40 mg/0.4 ml, 0.400 ml and/or 40 mg/0.8 ml, 0.800 ml (initial (maximum) contract price: RUB 4,490,862.25); and
- **Laronidase**, concentrate for solution for infusion, 100 U/ml, 5 ml (initial (maximum) contract price: RUB 625,007,593.50).

Thus, for the additional high-cost nosologies, the Ministry of Health of Russia initially purchased seven medicine items, two of which were in different dosage forms. The total initial contract price was RUB 3,807,562.013.1 (approx. RUB 3.8 billion), or about USD 56.8 million.

Taking into account the importance of the import substitution policy for the Russian pharmaceutical market, attention should be paid to the currently the only domestically produced medicine for the treatment of one of the five additional high-cost diseases – type II mucopolysaccharidosis.

The Idursulfase beta is intended for the treatment of Type II Mucopolysaccharidosis (Hunter's disease) and is a reference medicine registered in Russia in early 2018 under the trade name "Hanterase" by the Russian biopharmaceutical company Nanolek in cooperation with one of the largest biotechnological companies in Asia, South Korean GreenCross.^[7]

Type II mucopolysaccharidosis (Hunter's disease) is an orphan disease that usually affects only boys, but to date, there have been rare cases of illness in the girls described in the world.

Hunter's disease manifests itself at an early age of 2-4 years with a thickening of the nostrils, lips, tongue, joint stiffness, growth retardation, damage to the internal organs of the heart, liver, and intellectual retardation, especially in severe forms. In severe forms of the disease, patients quickly die at an early age, but with mild and moderate severity of the disease, with a timely and specific treatment, life expectancy can reach 40 – 50 years.

In Russia, more than 100 patients are currently diagnosed with Hunter syndrome, many of whom do not receive the necessary treatment. Every year, the number of patients diagnosed with Hunter syndrome increases throughout the world and in Russia. In general, it is important to note the positive trend of import substitution in the Seven High-Cost Nosologies segment as a result of the current pharmaceutical industry development strategy Pharma-2020, which led to an increase in the share of Russian medicine from 10.2% in 2012 to 39.19% in 2018 (Draft Strategy for Development of the Pharmaceutical Industry of Russian Federation until 2030).

The Government Decree No. 1416 dated November 26, 2018, approved the Rules for organizing the supply of medicines to people with cost-demanding diseases and the Rules for maintaining the Federal Register of such patients.

The rules establish the procedure for organizing the provision of medicines, as well as the procedure and conditions for the transfer of medicines into the ownership of Russian entities.

The budget allocations provided in the federal budget are the source of funding to organize the provision of patients with medicines. The patient's right for provision with medicines arises from the date of inclusion of information about him/her in the regional segment of the Federal Register, and the prescription and provision are made within no more than 20 working days from the date of inclusion.

No later than November 1 of the current year, the authorities of the entities of Russia in the field of health care will submit to the Ministry of Health of Russia applications for the supply of medicines with a justification for their volume, as well as a list of recipient organizations.

The need (scope of supply) for medicine is determined to take into account clinical recommendations (treatment protocols), and the average course dose of the medicine based on the actual monthly need and the need to form stock for 15 months.

It is important to note in the norm according to which Ministry of Health of Russia monitors the movement and accounting of medicines in the constituent entities of Russia, including information about the absence of need for individual medicines or the emergence of additional needs, and coordinates the redistribution of medicines among the constituent entities.

Information about patients is included in the regional segment of Federal Register by a medical organization at their place of residence or place of stay (if the period of stay exceeds six months) based on medical documents (their copies) or an extract from them.

The information about the patients with hemolytic-uremic syndrome, systemic-onset juvenile arthritis, and mucopolysaccharidosis of types I, II, and VI is included in the register based on the medical documents or their copies and extracts from them received from the federal medical organization.

The information is placed in Federal Register with the use of enhanced qualified electronic signature as per Federal Law on Electronic Signature.

In conclusion, it should be noted that all the subjects of medicine circulation according to the list of the seven nosologies should be registered in the system of monitoring the movement of medicines from July 1, 2019, to July 8, 2019.

The information about the medicines and all related operations will be introduced in the monitoring system starting from October 1, 2019 (Decree of the Government of Russia No. 1557 dated December 14, 2018, Decree of the Government of Russia No. 1556 dated December 14, 2018).

Discussion

It is important to note that many government officials and opinion leaders in healthcare and pharmacy support the federalization of financing rare diseases in the future since it is now very difficult for territorial entities of Russia to fulfill their authority to finance such diseases.

It is also necessary to focus on the information of the Ministry of Health of Russia about the tendency of growth in the number of patients with seven existing cost-demanding nosologies, which accordingly requires an increase in funding.

According to the authors, in the near future, the improvement of medicine provision of high-cost nosologies in Russia will be associated with the development of the national institute of medicine interchangeability, the functioning of the Common Market of Medicines of the Eurasian Economic Union, as well as the development strategy of the Russian pharmaceutical industry "Pharma 2030".^[8-12]

Conclusion

The increasing progress in science and technology has created wide changes in the provision of health services, which has led to the need for retraining in order to maintain competencies.^[13] At the end of 2018, the president of Russia Vladimir Putin approved a list of instructions on increasing the effectiveness of the medicine supply system for the population in the Russian Federation (approved by the president of Russia on December 17, 2018, No. Pr-2420).

The government of Russia is obliged once every six months to submit proposals for improving the scheme of providing citizens with medicines for the treatment of life-threatening and chronic progressive rare diseases. This should provide the measures of state support for domestic manufacturers of orphan medicines, as well as the possibility of concluding state contracts for the supply of such medicines for three years.

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