MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

INSTRUCTION
FOR USE OF THE MEDICINAL PRODUCT

Glurazyme

*/Stamp: MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION * LP-005297–170119 (ЛП-005297–170119) * AGREED/*

Registration number:

Trade name: Glurazyme

International non-proprietary name or group name: Imiglucerase

Dosage form: Lyophilizate for solution for infusion

Composition: a vial of lyophilizate contains

active ingredient:

imiglucerase 200 U* or 400 U*

excipients:

mannitol, sodium citrate dihydrate,
citric acid monohydrate,
polysorbate 80

* U is the amount of imiglucerase necessary to catalyse the hydrolysis of 1 μmol of the synthetic substrate para-nitrophenyl-β-D-glucopyranoside (pNP-Glc) per 1 min at (37 ± 0.2)°C.

Appearance

Lyophilizate: white to slightly yellowish amorphous mass

Reconstituted solution: clear or opalescent, colourless to slightly yellowish solution

Pharmacotherapeutic group: enzymes

ATC code: A16AB02

Pharmacological Properties

Pharmacodynamics

Gaucher disease is a rare autosomal recessive metabolic disease caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase. This enzyme catalyses the hydrolysis of glucosylceramide, a key component of the lipid structure of cell membranes, to glucose and ceramide. In patients with Gaucher disease, insufficient degradation of glucosylceramide leads to accumulation of a large amount of this substrate in the lysosomes of macrophages (known as

"Gaucher cells") resulting in widespread secondary pathological changes. Gaucher cells are usually found in the liver, spleen and bone marrow, and occasionally in the lungs, kidneys and intestines. From the clinical point of view, Gaucher disease is characterised by a heterogeneous phenotypic spectrum. The most common manifestations of the disease are hepatosplenomegaly, thrombocytopenia, anaemia and pathological changes in bone tissue. The latter are often the most disabling manifestations of Gaucher disease. They include bone marrow infiltration, osteonecrosis, bone pain and bone crises, osteopenia and osteoporosis, pathological fractures and impaired bone growth. Gaucher disease is associated with increased glucose production and increased degree of resting energy expenditure which may contribute to increased fatigue and cachexia. Patients with Gaucher disease may also demonstrate mild signs of inflammation. Besides, Gaucher disease is associated with an increased risk of dysproteinemia in the form of hypergammaglobulinemia, polyclonal gammopathy, monoclonal gammopathy of unknown etiology and myeloma. As a rule, the course of Gaucher disease is characterised by progression with the risk of development of irreversible complications in various organs over time. Clinical manifestations of Gaucher disease can adversely affect the quality of life. Gaucher disease is associated with the problem of increased morbidity and early mortality. In case of childhood onset of the disease signs and symptoms, the course of the disease is usually more severe. In paediatric patients, Gaucher disease may lead to growth retardation and delayed puberty.

Imiglucerase, the active ingredient of Glurazyme, is a modified form of β-glucocerebrosidase produced by recombinant DNA technology. Imiglucerase compensates for the enzyme deficiency by hydrolysing glucosylceramide, thus reversing the initial pathophysiological changes and preventing secondary pathological manifestations of the disease. Treatment with imiglucerase leads to a decrease in the size of the spleen and liver, improves or normalises blood platelets and red blood cells counts, improves or normalises the bone mineral density, reduces the bone marrow infiltration and reduces or stops bone pain and bone crises. Imiglucerase reduces the degree of resting energy expenditure. Imiglucerase has been shown to improve both mental and physical characteristics of the quality of life in patients with Gaucher disease. Imiglucerase reduces the level of chitotriosidase, a biomarker of glucosylceramide accumulation in macrophages and response to therapy. When used in paediatric patients, imiglucerase leads to normal pubertal development and catch-up growth which manifest as normal growth and normal bone mineral density in adulthood.

When administered at doses of 15 U/kg, 30 U/kg and 60 U/kg once every 2 weeks, the medicinal product induced positive dose-dependent effect with regard to the rate of improvement and the degree of both haematological and visceral manifestations (platelet count, haemoglobin concentration, liver and spleen size), as well as the bone tissue condition. As a rule, improvements occur more quickly in systems with a higher metabolic rate, for example, in peripheral blood, as

compared with those where this process is slower, such as bone tissue. For instance, the bone mineral density normalised after 8 years of treatment with imiglucerase at a dose of 60 U/kg once every 2 weeks, but such effect was not observed at lower doses of 15 U/kg and 30 U/kg once every 2 weeks. Imiglucerase at a dose of 60 U/kg once every 2 weeks reduced the severity of back pain after 3 months and the severity of bone crises within 12 months, while the bone mineral density improved within 24 months of therapy.

Therapy with Glurazyme at maintenance doses of 15–60 U/kg made it possible to maintain the baseline blood haemoglobin level and platelet count for the entire duration of therapy (1 year) in patients who had previously received imiglucerase. During that period, further reduction in the volume of spleen and a slight decrease in the volume of liver, as well as further improvement in the bone tissue condition were achieved.

Pharmacokinetics

As a result of intravenous infusions of imiglucerase at 4 various doses (7.5 U/kg, 15 U/kg, 30 U/kg, 60 U/kg of body weight) for 1 hour, steady-state enzymatic activity was achieved by 30 minutes. After the infusion it decreased rapidly, with the elimination half-life of 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 ml/min/kg (mean ± standard deviation, 14.5 ± 4.0 ml/min/kg). The volume of distribution corrected for patient's body weight varied from 0.09 to 0.15 l/kg (mean ± SD, 0.12 ± 0.02 l/kg). These parameters seem to be independent of the dose or duration of infusion, but each dose and infusion rate were only examined in 1 or 2 patients.

Therapeutic indications

Long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic type 1 Gaucher disease or chronic neuronopathic type 3 Gaucher disease, with clinically significant non-neurological manifestations of Gaucher disease, with one or several of the following symptoms:

- anaemia (after exclusion of other causes, such as iron deficiency)
- thrombocytopenia
- bone diseases (after exclusion of other causes, such as vitamin D deficiency)
- hepatomegaly or splenomegaly

Contraindications

Hypersensitivity to the active ingredient or any excipient of Glurazyme.

Use with caution

Caution shall be exercised when the product is used in patients with antibody formation or symptoms of hypersensitivity to Ceredase (alglucerase).

Posology and method of administration

For intravenous infusion.

Each vial of Glurazyme is intended for single use only.

Reconstitution and dilution of the medicinal product shall be performed using aseptic techniques.

After reconstitution and dilution, the product shall be administered by intravenous infusion. At initial infusions of Glurazyme, the infusion rate shall not exceed 0.5 U/kg/min. At subsequent administrations, the infusion rate may be increased, but it shall not exceed 1 U/kg/min. The infusion rate shall be increased under supervision of a healthcare professional.

Infusion of Glurazyme can be performed at home in patients with good tolerability of the product observed for several months. The decision on the possibility of home administration of the product shall be based on the respective evaluation and recommendations of the attending physician. Infusion of the medicinal product by the patient or a caregiver requires training provided by a healthcare professional in a clinical setting. The infusion technique and the necessity to keep a diary shall be explained to the patient or a caregiver.

In case of adverse events during the infusion, a patient shall immediately **stop the infusion** and seek medical attention. Subsequent infusions in a clinical setting may be required. When performed at home, the dose and frequency of infusions shall not be changed. Any changes are only possible under the supervision of a healthcare professional.

Due to heterogeneity and multisystemic nature of Gaucher disease, the dosage regimen shall be individualised for each patient and shall be based on a comprehensive assessment of clinical manifestations of the disease. The dose and frequency of administration of the medicinal product can only be corrected after a clear evaluation of the patient's individual response to the treatment (with regard to all respective clinical manifestations of the disease), either for maintenance of the achieved optimal parameters of clinical condition, or for further improvement of clinical parameters which have not yet been normalised.

Various dosage regimens have shown efficacy in terms of some or all non-neurological manifestations of the disease. Administration of initial doses of 60 U/kg once every 2 weeks has demonstrated an improvement in haematological and visceral parameters during 6 months of therapy, and continued treatment resulted in the arrest of progression or reduction of severity of bone lesions. Administration of doses of 15 U/kg once every 2 weeks has demonstrated an improvement in haematological parameters and a decrease in organomegaly but did not affect the osseous system parameters. The usual frequency of infusions is once every 2 weeks; the majority

of available data is related to this frequency. Maintenance therapy once every 4 weeks at the same cumulative dose as for the therapy once every 2 weeks can be therapeutically justified in some adult patients with persistent residual manifestations of type 1 Gaucher disease. However, existing clinical data are insufficient.

Paediatric population

No dose adjustment is required for paediatric patients.

Pregnancy and lactation

According to the limited data on the outcomes of 150 pregnancies (mainly based on spontaneous reports and literature data), administration of imiglucerase helps to control Gaucher disease during pregnancy. Also, these data did not confirm foetal toxicity of imiglucerase causing malformations, though statistical data were insufficient. Reports on foetal death were rare, and it is not known for sure whether these cases were associated with administration of imiglucerase or with Gaucher disease. There is only one known case of single dose administration of the medicinal product Glurazyme in a female patient during the first trimester of pregnancy. In this case there were no abnormalities in the course of pregnancy, and it resulted in birth of a healthy child.

No non-clinical studies in animals aimed at evaluation of the effect of imiglucerase on pregnancy, embryonal or foetal development, delivery and postnatal development were performed. There are no data on transplacental penetration of imiglucerase and its effect on a foetus during development.

In each case, evaluation of the risk-benefit ratio shall be performed in female patients with Gaucher disease who are pregnant or are planning pregnancy. A period of increased activity of Gaucher disease may be observed in female patients with Gaucher disease during pregnancy and the postpartum period which is manifested by an increased risk of bone changes, exacerbation of cytopenia, bleeding and increased need for haemotransfusion. It is commonly known that pregnancy and breastfeeding have a stress impact on calcium metabolism in the mother's body and accelerate bone remodelling process. This may contribute to the degree of bone changes in patients with Gaucher disease.

Treatment-naive women shall be recommended to consider the possibility to start the therapy prior to conception in order to achieve the optimum general condition. Females receiving imiglucerase shall consider the possibility to continue the therapy during the entire period of pregnancy. Close monitoring of the course of pregnancy and clinical manifestations of Gaucher disease is required for individual dose adjustment of in accordance with the needs of a patient and her response to treatment.

There are no data on the excretion of the active ingredient of the medicinal product into breast milk, but during breastfeeding this enzyme is likely to enter the gastrointestinal tract of the child.

Reconstitution

Reconstitution of lyophilizate shall be performed using aseptic techniques.

The number of vials of lyophilizate, the contents of which shall be reconstituted to prepare the solution for infusion, shall be determined in advance. In some cases, a small dose adjustment is allowed in order to avoid underuse of the contents of vials. Rounding of a dose in accordance with the number of full vials is allowed in order to avoid significant changes in the monthly dose.

Remove the vial(s) of lyophilizate from the refrigerator. Use a syringe with a needle to add **5.1 ml** (activity — 200 U) or **10.2** ml (activity — 400 U) of water for injection to the vial(s), directing the water at the wall of the vial. Foam may form when water contacts with the lyophilizate. Gently rotate the vial until complete dissolution of lyophilizate and allow to stand for about 5 minutes to let the foam settle. Visually inspect the reconstituted solution. It must be clear or opalescent, colourless or slightly yellowish and free of visible particulate matter. Do not use the solution in the presence of visible foreign particles or discolouration.

The reconstituted solution contains 40 U/ml of imiglucerase. The extractable volume of the reconstituted solution in each vial amounts to 5.0 ml (activity — 200 U) or 10.0 ml (activity — 400 U).

Use the reconstituted solution immediately. Should the infusion be delayed for any reason, the reconstituted solution can be stored in a dark place for not more than 24 h at 2–8°C, without freezing, or at not more than 25 °C for not more than 8 h, provided that the solution was prepared under controlled aseptic conditions. The expert preparing the solution is responsible for the conditions and duration of its storage. Once the said period is over, the unused reconstituted solution must be discarded.

Dilution

Solution for infusion must be prepared using aseptic techniques. Depending on the prescribed dose, combine reconstituted solutions from several vials with the respective activity. Transfer the calculated volume of the reconstituted solution from the vial(s) to an infusion vial/bag containing 0.9% sodium chloride solution for infusion in the volume of 100–200 ml. For mixing, invert the infusion vial/bag carefully for 1 min in order to avoid foam formation and start the intravenous infusion.

Use the prepared solution for infusion immediately.

The unused solution for infusion and used medical consumables must be discarded.

Undesirable effects

In some cases, treatment with imiglucerase may cause development of adverse reactions, the incidence of which is presented in the table. Adverse reactions are classified by organ class and incidence (common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000).

Adverse reactions in each group are listed in the descending order of their severity.

Nervous system disorders	Uncommon	Dizziness, headache, paraesthesia*
Cardiac disorders	Uncommon	Tachycardia*, cyanosis*
Vascular disorders	Uncommon	Hot flushes*, hypotension*
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, cough*
Gastrointestinal disorders	Uncommon	Vomiting, nausea, abdominal cramping, diarrhoea
Immune system disorders	Common	Hypersensitivity reactions
	Rare	Anaphylactic reactions
Skin and subcutaneous tissue disorders	Common	Urticaria/angioedema*, pruritus*, rash*
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, back pain*
General disorders and administration site conditions	Uncommon	Discomfort, burning sensation and oedema at the injection site, sterile abscess at the injection site, chest discomfort*, fever, chills, fatigue

Hypersensitivity symptoms (indicated by * in the table above) were reported in approximately 3% of patients. They were reported during or immediately after infusions. As a rule, such symptoms can be reversed using antihistamines and/or glucocorticoids, and in case of their occurrence patients shall stop infusion of the medicinal product and contact the attending physician.

Overdose

No cases of imiglucerase overdose have been reported. Imiglucerase was used at doses up to 240 U/kg once every 2 weeks.

Interaction with other medicinal products and other forms of interaction

No studies of interaction of the product with other medicinal products have been performed. Thus, the product shall not be combined with other medicinal products.

Special warnings and precautions for use

During management of patients with Gaucher disease, attending physicians must consult with physicians experienced in therapy of this disease.

This medicinal product contains sodium and shall be administered intravenously upon dilution with 0.9% sodium chloride solution. Upon dilution, the solution for infusion contains 0.62 mM of sodium (200 U/5 ml) or 1.24 mM of sodium (400 U/10 ml). This shall be taken into consideration by patients on a low-salt diet.

Therapeutic efficacy of the medicinal product shall be assessed individually for each patient. Recommended standard monitoring of a patient's condition during therapy with imiglucerase includes the following procedures: measurement of haemoglobin level and platelet count once in 3 months, measurement of spleen and liver size (CT or MRI) once in 12 months, total femur MRI, femur and spine X-ray, densitometry once in 12 months, as well as determination of metabolic biomarkers, such as chitotriosidase, once in 3 months.

Considering the severity of Gaucher disease prior to treatment, symptoms and a patient's age, the frequency and scope of examination may be changed, at the discretion of the attending physician. Upon achievement of therapeutic goals and after thorough assessment by the attending physician, the frequency of monitoring may be decreased.

<u>Hypersensitivity</u>

The data obtained using screening enzyme-linked immunosorbent assay (ELISA) and confirmed during radioimmune precipitation assay suggest that during the first year of therapy IgG antibodies to imiglucerase are formed in about 15% of patients receiving the therapy. Presumably, the formation of IgG antibodies in such patients takes place during the first 6 months of therapy, and cases of formation of anti-imiglucerase antibodies after 12 months of therapy are rare. Thus, in case of a suspected decrease in response to therapy it is recommended to perform periodic monitoring of the level of IgG anti-imiglucerase antibodies, as the presence of anti-imiglucerase antibodies increases the risk of hypersensitivity. In case of suspected hypersensitivity reactions in patients, it is recommended to perform a test for anti-imiglucerase antibodies.

Similarly to the use of other intravenous protein products, there is a possibility of development of severe allergic hypersensitivity reactions on rare occasions. In case of such reactions, infusion of the medicinal product shall be stopped immediately, and appropriate measures provided for by the effective medical standards for emergency treatment shall be taken.

If the formation of anti-Ceredase (alglucerase) antibodies or onset of hypersensitivity symptoms are detected in patients, precautions shall be taken during treatment with imiglucerase.

Pulmonary hypertension

Pulmonary hypertension is a well-known complication of Gaucher disease. Patients with a history of splenectomy are at a higher risk of developing pulmonary hypertension. In most cases, treatment with imiglucerase reduces the need for splenectomy, and early start of the therapy with imiglucerase decreases the risk of development of pulmonary hypertension. Regular examinations are recommended for detection of symptoms of pulmonary hypertension after diagnosing of Gaucher disease and further on. In particular, patients diagnosed with pulmonary hypertension must receive sufficient doses of imiglucerase for Gaucher disease control, and evaluation of the need for special pulmonary hypertension therapy shall be performed in such patients as well.

Effects on ability to drive and use machines

No studies of the effects of the medicinal product on the ability to drive and use machines requiring enhanced concentration have been performed.

Presentation

Lyophilizate for solution for infusion, 200 U or 400 U, in glass vials with rubber stoppers and tamper-evident flip-off aluminium-plastic cap.
One vial with the instruction for use in a carton.

Shelf life

2 years
Do not use after the expiry date indicated on the package.

Storage conditions

Protected from light, at 2–8°C.
Keep out of reach of children.

Terms and conditions of sale

On prescription only.

Marketing authorisation holder

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