MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

MEDICINAL PRODUCT LABEL
LONGIDAZA®

Registration Number: LS-000764

Trade name: Longidaza®

International non-proprietary or generic name: Bovhyaluronidase azoximer (bovhyaluronidasum azoximerum)

Chemical name: Conjugate of hyaluronidase with 1,4-ethylenepiperazine N-oxide and (N-carboxymethyl)-1,4-ethylenepiperazine bromide copolymer

Dosage form: Lyophilized powder for solution for injection

Composition per 1 vial:

Active ingredient: Bovhyaluronidase azoximer (Longidaza®) 3000 IU

Excipient: Mannitol up to 20 mg

Description: Porous mass, white to white-yellowish or white-brownish, hygroscopic.

Pharmacotherapeutic group: Enzymatic agent

ATC code: V03AX

Pharmacological properties

Pharmacodynamics:

Bovhyaluronidase azoximer is a conjugate of proteolytic enzyme hyaluronidase with a high molecular weight carrier from the group of N-oxide derivatives of poly-1,4-ethylenepiperazine. Bovhyaluronidase azoximer possesses the full spectrum of pharmacological properties inherent in medicinal products with hyaluronidase activity. Specific substrates of hyaluronidase are glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate) that are the “cementing” agents of connective tissues. Hydrolysis (depolymerization) reduces the viscosity of glycosaminoglycans, and their ability to bind water and metal ions. It helps to increase tissues permeability, improve their trophism; promotes swelling reduction, dissolution of hematomas, and elimination of contractures and adhesions; increases scar-modified sites elasticity and joint mobility. The effect is most pronounced in the initial stages of a pathological process.

The clinical effect of bovhyaluronidase azoximer is significantly higher than that of native hyaluronidase. Conjugation improves the enzyme resistance to temperature and inhibitors

exposure, increases its activity and leads to prolonged action. The enzymatic activity of bovhyaluronidase azoximer is maintained at 37°C for 20 days, while native hyaluronidase under the same conditions loses its activity within 24 hours. Bovhyaluronidase azoximer also retains the pharmacological properties of a carrier with chelating, antioxidant, anti-inflammatory and immunomodulatory activity. Bovhyaluronidase azoximer is able to bind the iron ions, promoters of free radical reactions, inhibitors of hyaluronidase and stimulators of collagen synthesis that are released during the hydrolysis of glycosaminoglycans, and thereby suppress the reverse reaction aimed at the synthesis of components of connective tissue. The polytropic properties of bovhyaluronidase azoximer are realized in a pronounced anti-fibrotic effect; it has been experimentally proven by biochemical, histological and electron microscopic studies on a model of pneumofibrosis.

Bovhyaluronidase azoximer regulates (increases or reduces depending on the baseline level) the synthesis of inflammatory mediators (interleukin-1 and tumor necrosis factor alpha); it is able to attenuate the course of the acute phase of inflammation, increase the humoral immune response and the body's resistance to infection. These properties allow the use of bovhyaluronidase azoximer during or after surgical treatment to prevent hypertrophic scarring and adhesions. At therapeutic doses, during or after surgical treatment, bovhyaluronidase azoximer does not cause deterioration in the postoperative period or progression of the infectious process; neither it slows down the recovery of bone tissue.

Bovhyaluronidase azoximer increases the absorption of drugs when co-administered subcutaneously or intramuscularly, and accelerates the anesthetic effect of local anesthetics.

Bovhyaluronidase azoximer is a practically non-toxic compound, it does not impair the normal functioning of the immune system, does not affect the reproductive function of male and female rats, pre- and postnatal development of offspring, and is not mutagenic or carcinogenic. Bovhyaluronidase azoximer has been experimentally proven to reduce the irritant and allergenic properties of the hyaluronidase enzyme. At therapeutic doses, bovhyaluronidase azoximer is well-tolerated by patients.

Pharmacokinetics:

During parenteral administration, bovhyaluronidase azoximer is rapidly absorbed into the systemic circulation, reaches its maximum blood concentration within 20–25 minutes, and is characterized by a high rate of distribution in the body. The half-life is about 0.5 hours, the half-life (T½) with intramuscular administration is 36 hours, with subcutaneous administration is about 45 hours. The

apparent volume of distribution is 0.43 L/kg. Conjugation does not reduce the high bioavailability of the enzyme — bioavailability is not less than 90%.

The active ingredient penetrates all organs and tissues, including through the blood-brain and blood-ocular barriers.

In the body, hyaluronidase is subjected to hydrolysis, and the carrier breaks down to low molecular weight compounds (oligomers), which are excreted primarily through the kidneys in two phases. During the first day, 45–50% is excreted through the kidneys, and no more than 3% is excreted through the intestines. Then the excretion rate slows down, and by the 4th or 5th day the drug is completely eliminated.

Indications for use:

In adults as part of combination therapy for the treatment and prevention of diseases associated with connective tissue hyperplasia:

In gynecology: treatment and prevention of adhesions in the pelvis in inflammatory diseases of the internal genital organs, including tubal-peritoneal infertility, uterine synechiae, chronic endometritis.

In urology: treatment of chronic prostatitis, interstitial cystitis.

In surgery: treatment and prevention of adhesions after surgical interventions on the abdominal organs, and long-term non-healing wounds.

In dermatovenerology and cosmetology: treatment of localized scleroderma, non-infectious onychodystrophy, keloid, hypertrophic scars after pyoderma, injuries, burns, surgeries, grade II-IV acne vulgaris with scarring (post-acne).

In pulmonology and phthisiology: treatment of pneumosclerosis, fibrosing alveolitis, tuberculosis (cavernous-fibrous, infiltrative, tuberculoma).

In rheumatology: treatment of joint contractures, including Dupuytren's contractures and flexion tendon contractures of the hand, arthrosis, ankylosing spondylitis, hematomas.

To increase bioavailability: co-administered with antibacterial drugs in urology, gynecology, surgery, dermatovenerology, pulmonology, to enhance the effect of local anesthetics.

Contraindications:

- hypersensitivity bovhyaluronidase azoximer and other components of the drug;
- acute infectious conditions without the combined use of antimicrobial agents;

- pulmonary hemorrhage and hemoptysis;
- recent vitreous hemorrhage;
- malignant neoplasms;
- acute renal failure;
- age under 18 years (no efficacy and safety data available);
- pregnancy and breastfeeding.

Contraindications when administering the drug using physiotherapy procedures:

- hypersensitivity to laser radiation and ultrasound;
- photodermatitis;
- patient taking steroid hormonal drugs;
- inflammatory process in the joint area;
- somatic diseases in which physiotherapy procedures are contraindicated.

Safety precautions:

- Chronic renal failure (use no more than once a week).

Use during pregnancy and breastfeeding:

Longidaza® is contraindicated in pregnant and breastfeeding women.

Method of administration and dosage

Longidaza® can be administered subcutaneously, intramuscularly, or externally.

Methods of administration are selected by the physician depending on the diagnosis, severity and clinical course of the disease.

Preparation of solution:

1. For subcutaneous or intramuscular administration, dissolve the contents of the Longidaza® 3000 IU vial in 1.0–2.0 mL of 0.5% procaine (novocaine) solution. In case of intolerance to procaine (novocaine), Longidaza® is dissolved in the same volume of 0.9% sodium chloride solution for injection or water for injection.

2. When used with photophoresis for onychodystrophy treatment, dilute the contents of the Longidaza® 3000 IU vial in 0.5 mL of distilled water, dissolve for 3–4 minutes, apply 1 drop (about 300 IU of Longidaza®) to the distal phalanges of the fingers.

3. To perform photophoresis or ultraphonophoresis in acne vulgaris treatment, dilute 1 vial of Longidaza® 3000 IU in 2–5 mL of ultrasound gel (“Mediagel-T”) and apply to the lesion.

4. For administration of the drug by ultrasound in the treatment of contractures, dissolve the contents of the Longidaza 3000 IU vial in 1.0 mL of saline solution, mix with 5–7 g of petroleum jelly and apply to the scar area.

5. When used to increase bioavailability, dissolve the contents of the Longidaza® 3000 IU vial in 2.0 mL of 0.9% sodium chloride solution for injection.

The solvent must be introduced into the vial slowly, kept for 2–3 minutes, and stirred gently without shaking, so as not to foam the protein.

The prepared solution for parenteral administration is not to be stored.

Do not administer intravenously!

Recommended prevention and treatment regimens

- ***For the prevention*** of peritoneal adhesions and hypertrophic scarring after surgical interventions on the abdominal cavity and pelvic organs administer 3000 IU intramuscularly once every 3 days for a course of 5 injections. If necessary, Longidaza® can be continued in a total of up to 10 injections administered once every 5 days.
- ***For treatment***

In gynecology:

- In adhesions in the pelvis in inflammatory diseases of the internal genital organs administer 3000 IU intramuscularly once every 3–5 days, for a course of 10–15 injections.

- In tube-peritoneal infertility administer 3000 IU intramuscularly in a total of up to 15 injections: first 5 injections once every 3 days, then once every 5 days.

In urology:

- In chronic prostatitis administer 3000 IU intramuscularly once every 5 days, for a course of 10—15 injections.

- In intramuscular interstitial cystitis administer 3000 IU once every 5 days, for a course of up to 10 injections.

In surgery:

- In peritoneal adhesions after surgical interventions on the abdominal organs administer 3000 IU intramuscularly once every 3–5 days for a course of 10–15 injections.

- In long-term non-healing wounds administer 3000 IU intramuscularly once every 5 days, for a course of 5–10 injections.

In dermatovenerology, cosmetology:

- In localized scleroderma administer intramuscularly once every 3-5 days, for a course of up to 20 injections. The dose and course are selected individually depending on the clinical course, stage, localization of the disease and individual characteristics of the patient.
- In non-infectious onychodystrophy: apply 1 drop of the prepared solution (approximately 300 IU of Longidaza®) to the projection area of the posterior nail fold; immediately after performing exposure to low-intensity infrared laser radiation with a pulse repetition rate of 80–1500 Hz, pulse duration of 110–160 ns, and pulse power of 4–6 W/pulse. Photophoresis is performed according to a contact-stable technique, 1 minute per field, total exposure time is up to 10 minutes for isolated nail lesions of the hands or feet and up to 20 minutes for combined nail lesions of the hands or feet. The course of 15 procedures, daily.
- In keloid, hypertrophic and developing scars after pyoderma, burns, surgeries, injuries: Intraruminal or subcutaneous administration near the site of injury once every 3 days, for a course of up to 15 injections. The dilution volume of Longidaza® is selected by the doctor depending on the number of injection sites. If necessary, the course can be continued according to the schedule once every 5 days for up to 25 injections. Depending on the area of skin lesion, the age of scar formation, it is possible to alternate subcutaneous and intramuscular administration once every 5 days for a course of up to 20 injections.
- In grade II–IV acne vulgaris with scarring (post-acne): intramuscularly 3000 IU, 2 injections per week for a course of up to 10 injections.

Longidaza® can be administered by photophoresis or ultraphonophoresis daily, 5 days a week for 3 weeks, 15 sessions per course. Apply the prepared solution to the affected area and immediately after performing exposure to low-intensity infrared laser radiation with a pulse repetition rate of 80–1500 Hz or ultrasound with a frequency of 880 kHz –1 MHz in a continuous or pulsed mode. When the lesion is localized on the face, the intensity of ultrasound exposure is 0.2–0.4 W/cm^2. Depending on the area of exposure, use a small emitter of 1 cm^2, a medium-sized emitter of 2 cm^2 or a large emitter of 4 cm^2. The method of exposure is contact labile. The total exposure area must not exceed 50 cm^2. Total exposure time is 5 minutes.

In pulmonology and phthisiology:

- In pneumosclerosis administer 3000 IU intramuscularly once every 5 days for a course of 10 injections.
- In fibrosing alveolitis administer 3000 IU intramuscularly once every 5 days for a course of 15 injections, then use as maintenance therapy once every 10 days in a total of up to 25 administrations.
- In tuberculosis administer 3000 IU intramuscularly once every 5 days, for a course of up to 25 injections. Depending on the clinical picture and the severity of the disease, long-term therapy is possible (from 6 months to 1 year once every 10 days).

In rheumatology:

- In joint contractures, including Dupuytren's contractures and flexion tendon contractures of the hand: administer subcutaneously into the contracture area at 3000 IU once a day, daily for 5 days with a further break for two days, for a course of up to 15 injections. Repeat course in 1.5 months. In case of local reactions to injection, Longidaza® can be administered by phonophoresis on the contracture area, every other day, 3 times a week, for a course of up to 12 procedures. The prepared solution is applied to the scar area, and the ultrasound probe is used according to the labile technique at an ultrasound intensity of 0.2 W/cm2, in continuous mode; the duration of the procedure is 10 minutes. Repeat course in 1.5 months.
- In arthrosis, ankylosing spondyloarthritis administer 3000 IU subcutaneously near the lesion site once every 3 days, for a course of up to 15 injections; if necessary, treatment can be continued with injections once every 5 days. The duration of maintenance therapy is chosen by the doctor depending on the severity of the disease.
- In hematomas administer 3000 IU subcutaneously near the lesion once every 3 days, for a course of up to 5 injections.

Adverse reactions:

Classification of adverse reactions by organs and systems with the indication of their frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000), including individual reports, frequency unknown (frequency cannot be estimated based on available data).

Skin and subcutaneous tissue disorders. Uncommon: skin redness, itching and swelling at the injection/application site. All local reactions disappear within 48–72 hours.

General disorders and administration site conditions. Common: tenderness at the administration

site.

Immune system disorders. Very rarely: allergic reactions, including immediate type.

Laboratory and instrumental data. Very rare: an increase in body temperature is possible.

If you notice any adverse reactions that are not listed in the instructions, please inform your physician.

Overdose:

Symptoms of overdose may manifest as chills, fever, dizziness, decreased blood pressure. Drug is discontinued and symptomatic therapy is prescribed.

Drug-drug interaction:

Longidaze® can be used in combination with antibiotics, antiviral and antifungal drugs, broncholytics.

When used in combination with other medicinal products (antibiotics, local anesthetics, diuretics), Longidaza® increases bioavailability and enhances their effect. Enzymatic activity of Longidaza® may be reduced when co-administered with heparin, high doses of non-steroidal anti-inflammatory drugs (NSAIDs), cortisone, adrenocorticotropic hormone (ACTH), estrogens or antihistamines.

Longidaza® should not be co-administered with furosemide, benzodiazepines, phenytoin and adrenaline.

Special indications:

In case of allergic reaction Longidaze® discontinue the drug and seek medical help.

If treatment with Longidaza® needs to be discontinued, it can be done immediately, without titration.

If you miss the next dose of the drug, please administer the next dose as usual as indicated in the instructions or by your physician. Please do not administer a double dose to compensate for the missed doses.

Do not use the drug product if there are visual signs of its unsuitability (packaging defect or powder discoloration).

Longidaza® should not be administered in the area of acute infectious inflammation due to the risk of localized infection spreading.

In case of treatment of diseases accompanied by a severe chronic productive process in the

connective tissue, long-term maintenance therapy with Longidaza® 3000 IU with 10–14 days intervals between injections is recommended after the standard course.

Effects on ability to drive and use machines:

The use of the drug product does not affect the ability to perform potentially dangerous activities that require increased concentration and rate of psychomotor reactions (driving vehicles, working with moving mechanisms, dispatcher and operator duties).

Formulation:

Lyophilized powder for solution for injection.

20 mg per 3 mL dark glass vials of hydrolytic class 1. 5 vials per blister of polyvinyl chloride film. One blister together with the Instructions for Use is placed in a carton pack.

Shelf life:

2 years. Do not use after the expiration date.

Storage conditions:

Store at a temperature not exceeding 8°C. Do not freeze.

Keep out of reach of children.

Prescription status:

Available on prescription.

Manufacturer / legal entity that obtained the marketing authorization:

Manufacturer and marketing authorization holder:

NPO Petrovax Pharm, LLC

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