Longidaza®

Longidaza Injections Instruction

International Non-Proprietary Name (INN): bovhyarulonidase azoximer

Dosage form: solution for injections

Structure
Active ingredient: bovhyaluronidase azoximer (Longidaze®) – 3000 IE;
Excipients: mannitol - up to 20 mg.

Description
Lyophilizate for injection solution preparation in the form of a porous mass of white color or white color with a yellowish or brownish hue, hygroscopic.

Pharmacological classification: enzyme agent

ATC code: V03AX

Pharmacological action: enzyme agent

Pharmacodynamics

Longidaze® is a conjugate of the proteolytic enzyme hyaluronidase with a high-molecular-weight carrier from the group of poly-1,4-ethylene-piperazine N-oxide derivatives. Longidaze® possesses the full spectrum of pharmacological properties inherent in drugs with hyaluronidase activity. The specific substrates of hyaluronidase are glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate) - the "cementing" substance of connective tissue. As a result of hydrolysis (depolymerization), the viscosity of glycosaminoglycans decreases, their ability to bind water and metal ions decreases. As a consequence, tissue permeability increases, their trophism improves, edema decreases, hematomas dissolve, the elasticity of scar-modified areas increases, contractures and adhesions disappear, and joint mobility increases. The effect is most pronounced in the early stages of the pathological process.

The clinical effect of Longidaze® is significantly higher than that of native hyaluronidase. Conjugation increases the stability of the enzyme to the action of temperature and inhibitors, increases its activity, and leads to a prolonged action. The enzymatic activity of Longidaze® is maintained when heated to 37°C (98.6° F) for 20 days, while native hyaluronidase under these conditions loses its activity within a day. Longidaze® also retains the pharmacological properties of the carrier, which has chelating, antioxidant, anti-inflammatory, and immunomodulatory activities.

Longidaze® is capable of binding iron ions released during glycosaminoglycan hydrolysis - activators of free radical reactions, hyaluronidase inhibitors, and collagen synthesis stimulators, thereby suppressing the reverse reaction aimed at synthesizing connective tissue components. The polytropic properties of Longidaze® are realized in its pronounced antifibrotic action, experimentally proven by biochemical, histological, and electron microscopic studies on a pneumofibrosis model.

Longidaze® regulates (increases or decreases depending on the initial level) the synthesis of inflammatory mediators (interleukin-1 and TNF-α), is capable of attenuating the acute phase of inflammation, enhancing humoral immune response, and increasing the body's resistance to infection. These properties allow using Longidaze® during or after surgical treatment to prevent severe scarring and adhesion formation. The use of Longidaze® in therapeutic doses during or after surgery does not worsen the course of the postoperative period or the progression of the infectious process; it does not delay bone tissue recovery.

When administered subcutaneously or intramuscularly, Longidaze® increases the absorption of drugs and accelerates pain relief when local anesthetics are administered.

Longidaze® is practically non-toxic, does not disturb the normal functioning of the immune system, does not affect the reproductive function of male and female rats, the pre- and postnatal development of offspring, and does not have mutagenic or carcinogenic effects. It has been experimentally proven that Longidaze® has reduced irritating and sensitizing properties compared to the hyaluronidase enzyme. In therapeutic doses, Longidaze® is well tolerated by patients.

Pharmacokinetics

When administered parenterally, Longidaze® is rapidly absorbed into the systemic circulation and reaches peak blood concentration within 20-25 minutes, characterized by a high rate of distribution throughout the body.

The half-life period is approximately 0.5 hours, with a half-life of elimination of 36 hours for intramuscular administration and around 45 hours for subcutaneous administration. The apparent volume of distribution is 0.43 L/kg. Conjugation does not reduce the enzyme's high bioavailability - the bioavailability is at least 90%.

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

In the body, hyaluronidase undergoes hydrolysis, and the carrier breaks down into low-molecular-weight compounds (oligomers), which are primarily excreted through the kidneys in two phases. During the first day, 45-50% is excreted via the kidneys, with no more than 3% excreted through the intestines. Subsequently, the rate of excretion slows down, and by 4-5 days, the drug is completely eliminated.

Intended uses

The drug is prescribed to adults as part of complex therapy for the treatment and prevention of diseases associated with connective tissue hyperplasia.

In gynecology:

Treatment and prevention of adhesion processes in the pelvic area in inflammatory diseases of the internal genital organs, including tuboperitoneal infertility, intrauterine adhesions, chronic endometritis.

In urology:

Treatment of chronic prostatitis; Treatment of interstitial cystitis.

In surgery:

Treatment and prevention of adhesion processes after surgical interventions on the organs of the abdominal cavity; Long-term non-healing wounds.

In dermatovenereology and cosmetology:

Treatment of limited scleroderma; Treatment of non-infectious onychodystrophy; Treatment of keloid, hypertrophic scars after pyoderma, trauma, burns, surgeries; Treatment of stage II-IV vulgar acne with scar deformities (post-acne).

In pulmonology and phthisiology:

Treatment of pneumosclerosis, fibrosing alveolitis; Treatment of tuberculosis (cavernous-fibrotic, infiltrative, tuberculoma).

In rheumatology:

Treatment of joint contractures (including Dupuytren's contracture and flexor tendon contractures of the hand), arthrosis, ankylosing spondylitis, hematomas.

For increasing bioavailability:

When combined with antibacterial drugs in urology, gynecology, surgery, dermatovenereology, pulmonology, to enhance the action of local anesthetics.

Contraindications

- Acute infectious diseases without concomitant use of antimicrobial agents;
- Pulmonary hemorrhage and hemoptysis;
- Fresh hemorrhage in the vitreous body;
- Malignant neoplasms;
- Acute renal failure;
- Age under 18 years (clinical trial data are not available);
- Pregnancy;
- Breastfeeding;
- Increased sensitivity to bovhyaluronidase azoximer and other components of the drug.

When administering the drug through physiotherapeutic procedures:

- Increased sensitivity to laser radiation and ultrasound exposure;
- Photodermatitis;
- Use of steroid hormonal drugs;
- Inflammatory process in the joint area;
- Somatic diseases for which physiotherapeutic procedures are contraindicated.

The drug should be used with caution in chronic renal failure (administered no more than once a week).

Dosage and administration

Longidaze® is administered subcutaneously, intramuscularly, or topically.

The method of administration is determined by the doctor depending on the diagnosis, severity, and clinical course of the disease.

1. *For subcutaneous or intramuscular injection*, the contents of the Longidaza® 3000 IU vial are dissolved in 1.0-2.0 ml of 0.5% procaine solution. In case of intolerance to procaine, the Longidaza® preparation is dissolved in the same volume of 0.9% sodium chloride solution for injections or water for injections.
2. When used with *phonophoresis* for the treatment of onychodystrophy, the contents of the Longidaza® 3000 IU vial are diluted in 0.5 ml of distilled water, dissolved for 3-4 minutes, and applied as 1 drop (about 300 IU of Longidaza® preparation) to the distal phalanges of the fingers.
3. For conducting *phonophoresis or ultra-phonophoresis* in the treatment of vulgar acne, 1 vial of Longidaza® 3000 IU is diluted in 2-5 ml of ultrasound gel (Mediagel-T) and applied to the lesion area.
4. For administration using *ultrasound* in the treatment of contractures, the contents of the Longidaza® 3000 IU vial are dissolved in 1.0 ml of physiological saline, mixed with 5-7 g of vaseline, and applied to the scar area.
5. When used to increase *bioavailability*, the contents of the Longidaza® 3000 IU vial are dissolved in 2.0 ml, and for a dose of 1500 IU in 1.0 ml of 0.9% sodium chloride solution for injections.

The solvent should be introduced slowly into the vial, allowed to stand for 2-3 minutes, gently mixed without shaking to avoid foaming of the protein. The prepared solution for parenteral administration should not be stored.

Do not administer intravenously.

Recommended prevention and treatment regimens:

For the prevention of adhesion disease and severe scarring after surgical interventions on the organs of the abdominal cavity and pelvis - intramuscularly at a dose of 3000 IU once every 3 days for a course of 5 injections. If necessary, the use of Longidaza® can be continued with a total course of up to 10 injections administered once every 5 days.

In gynecology:

- For the treatment of adhesion processes in the pelvis in inflammatory diseases of the internal genital organs - intramuscularly at a dose of 3000 IU once every 3-5 days, for a course of 10-15 injections;
- For the treatment of tuboperitoneal infertility - intramuscularly at a dose of 3000 IU, with a total course of up to 15 injections (the first 5 injections once every 3 days, then once every 5 days).

In urology:

- For the treatment of chronic prostatitis - intramuscularly at a dose of 3000 IU once every 5 days, for a course of 10-15 injections;
- For the treatment of interstitial cystitis - intramuscularly at a dose of 3000 IU once every 5 days, for a course of up to 10 injections.

In surgery:

- For the treatment of adhesion disease after surgical interventions on the organs of the abdominal cavity - intramuscularly at a dose of 3000 IU once every 3-5 days for a course of 10 to 15 injections;
- For the treatment of long-term non-healing wounds - intramuscularly at a dose of 3000 IU once every 5 days, for a course of 5-10 injections.

In dermatovenereology and cosmetology:

- For the treatment of localized scleroderma - intramuscularly at a dose of 3000-4500 IU once every 3-5 days, for a course of up to 20 injections. The dose and course are individually selected depending on the clinical course, stage, localization of the disease, and individual characteristics of the patient;
- For the treatment of non-infectious onychodystrophy, apply 1 drop of the prepared solution (approximately 300 IU of Longidaza® preparation) to the area of the projection of the posterior nail fold without a time interval, followed by exposure to low-intensity infrared laser radiation with a pulse repetition rate of 80-1500 Hz, pulse duration of 110-160 ns, at pulse power of 4-6 W/pulse. Photophoresis is performed using a contact-stable method, for 1 minute per field, with a total exposure time of up to 10 minutes in isolated nail lesions of the hands or feet, and up to 20 minutes in combined lesions of the nails of the hands or feet. The course consists of 15 procedures, daily;
- For the treatment of keloids, hypertrophic, and forming scars after pyoderma, burns, surgeries, traumas - intrascar or subcutaneous injection near the site of injury once every 3 days, for a course of up to 15 injections at a dose of 3000-4500 IU. The volume of dilution of the Longidaza® preparation is chosen by the doctor depending on the number of injection points. If necessary, the course can be continued according to the scheme once every 5 days for up to 25 injections. Depending on the area of skin damage and the age of scar formation, alternating subcutaneous and intramuscular injections once every 5 days at a dose of 3000 IU, for a course of up to 20 injections, are possible;
- For the treatment of vulgar acne of stages II-IV with scar deformity (post-acne) - intramuscularly, 2 injections per week, at a dose of 3000 IU, for a course of up to 10 injections.

The Longidaza® drug can be administered using the photophoresis or ultrafonophoresis procedure at a dose of 3000 IU daily, 5 days a week for 3 weeks, with 15 sessions per course. The prepared solution is applied to the affected area, and without a time interval, low-intensity infrared laser radiation with a pulse repetition rate of 80-1500 Hz or ultrasound with a frequency of 880 kHz - 1 MHz is applied in continuous or pulsed mode. When the lesion is localized on the face, the intensity of ultrasound exposure is 0.2-0.4 W/cm2. Depending on the area of exposure, a small emitter - 1 cm2, medium - 2 cm2, or large - 4 cm2 is used. The method of exposure is contact-labile.

The total area of exposure should not exceed 50 cm2. The total exposure time is 5 minutes.

In pulmonology and phthisiology:

- For the treatment of pneumosclerosis - intramuscularly at a dose of 3000 IU once every 5 days for a course of 10 injections;
- For the treatment of fibrosing alveolitis - intramuscularly at a dose of 3000 IU once every 5 days for a course of 15 injections, followed by maintenance therapy once every 10 days, for a total course of up to 25 injections;
- For the treatment of tuberculosis - intramuscularly at a dose of 3000 IU once every 5 days for a course of up to 25 injections. Depending on the clinical picture and severity of

the disease, long-term therapy is possible (from 6 months to 1 year at a dose of 3000 IU once every 10 days).

In rheumatology:

- For the treatment of joint contractures, including Dupuytren's contracture and flexor tendon contractures of the hand - subcutaneously into the area of contracture at a dose of 3000 IU once a day, daily for 5 days with a subsequent break of 2 days, for a course of up to 15 injections. A repeat course can be administered after 1.5 months. In case of local reactions to the injection of Longidaza®, the drug can be administered using the phonophoresis method to the area of contracture, 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 ultrasound is applied using a labile method with an ultrasound intensity of 0.2 W/cm2, in continuous mode, for a duration of 10 minutes. A repeat course can be administered after 1.5 months.
- For the treatment of osteoarthritis, ankylosing spondylitis - subcutaneously near the affected area at a dose of 3000 IU 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 determined by the physician depending on the severity of the disease.
- For the treatment of hematomas - subcutaneously near the affected area at a dose of 3000 IU once every 3 days, for a course of up to 5 injections.

Side effects

Classification of adverse reactions by organs and systems with indication of their frequency of occurrence: 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 isolated reports, frequency unknown (frequency cannot be estimated from available data).

Skin and subcutaneous tissue disorders: uncommon - skin redness, itching, and swelling at the injection/site of application. All local reactions resolve spontaneously within 48-72 hours.

General disorders and administration site conditions: common - pain at the injection site.

Immune system disorders: very rare - allergic reactions, including immediate type.

Laboratory and instrumental data: very rare - possible increase in body temperature.

If any adverse effects not listed in the instructions are observed, the patient should inform their doctor.

Overdose

Symptoms of overdose may include chills, fever, dizziness, and decreased blood pressure.

Treatment: Discontinue the administration of the drug and initiate symptomatic therapy.

Interaction with other drugs

Longidaza® can be combined with antibiotics, antiviral drugs, antifungal agents, and bronchodilators.

When used in combination with other medications (such as antibiotics, local anesthetics, diuretics), Longidaza® increases bioavailability and enhances their effects.

When used concomitantly with high doses of salicylates, cortisone, ACTH, estrogens, or antihistamine drugs, the enzymatic activity of Longidaza® may be reduced.

Longidaza® should not be administered simultaneously with furosemide, benzodiazepines, or phenytoin.

Precaution

If an allergic reaction develops, the patient should discontinue the use of Longidase® and seek medical attention.

If discontinuation of Longidase® is necessary, it can be stopped immediately without tapering the dose.

In case of missing a dose, the next dose of the medication should be administered according to the regular schedule as indicated in the instructions or as recommended by a physician. The patient should not double the dose to make up for missed doses.

Do not use Longidase® if there are visual signs of its unsuitability (such as packaging defects or changes in the color of the powder).

Avoid injecting Longidase® into areas of acute infectious inflammation due to the risk of spreading localized infection.

For the treatment of diseases associated with severe chronic productive processes in connective tissue, prolonged maintenance therapy with Longidase® 3000 IU is recommended after the standard course, with intervals between injections of 10-14 days.

Impact on the ability to drive and operate machinery:

The use of Longidase® does not affect the ability to perform potentially hazardous activities that require increased attention and rapid psychomotor reactions.

Pregnancy and lactation

The use of Longidase® is contraindicated in pregnant women and women who are breastfeeding.

Use in renal dysfunction

Use of the drug is contraindicated in acute renal failure.

In chronic renal failure, the drug is administered no more than once a week.

Storage conditions

Store in a dry, dark place at a temperature of 2°C to 8°C (35.6 to 46.4 F). Keep out of the reach of children.

Shelf life

2 years. Do not use after the expiry date.

Manufacturer

NPO Petrovax Pharm, LLC.