

THE MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION

INSTRUCTION

on medical use of medicinal product

LONGIDAZE®

<Seal: Russian Ministry of Healthcare
JIC-000764 July 19, 2016
AGREED>

Registration number: JIC-000764

Trade name: Longidaze®

International Nonproprietary Name: bovhyaluronidase azoximer (bovhyaluronidasum azoximerum)

Chemical name: hyaluronidase conjugate with co-polymer of N-oxide 1,4-ethylenepiperazine and (N-carboxymethyl)-1,4- ethylenepiperazine bromide

Pharmaceutical form: lyophilizate for solution for injection

Composition per 1 ampoule or bottle:

Active substance: bovhyaluronidase azoximer (Longidaze®) 1500 IU or 3000 IE

Excipient: mannitol up to 15 mg (for 1500 IE dose) or up to 20 mg (for 3000 IE dose)

Description: porous white or white with a yellowish or brownish tint mass, hygroscopic.

Pharmacotherapeutic group: enzymes

ATC code: V03AX

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Bovhyaluronidase azoximer is a conjugate of proteolytic enzyme hyaluronidase with high-molecular carrier from N-oxide derivatives group poly-1,4-ethylenepiperazine. Bovhyaluronidase azoximer possesses the full spectrum of pharmacological properties typical of medicinal products with hyaluronidase activity. Specific hyaluronidase substrate are glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate) – a “cementing” agent of connective tissue. Due to hydrolysis (depolymerization) decrease of glycosaminoglycans viscosity, ability to bind water and metal ions is observed. As a consequence, permeability of tissues increases, tissues trophism improves, edemas decrease, hematomas resolute, elasticity of skin areas changed by scars increases, contractures and commissures are removed, joints mobility increases. The most pronounced effect is observed in the early stages of pathological process.

Clinical effect of bovhyaluronidase azoximer is much higher than native hyaluronidase effect. Conjugation increases enzyme resistance to the influence of temperature and inhibitors, enhances its activity and leads to effect prolongation. Enzymatic activity of bovhyaluronidase azoximer is preserved at heating at 37°C during 20 days, while native hyaluronidase in the same conditions loses its activity during one day. Pharmacological properties of a carrier possessing chelating, anti-inflammatory and immunomodulating activity are also preserved in bovhyaluronidase azoximer. Bovhyaluronidase azoximer is able to bind releasing at glycosaminoglycans hydrolysis ferrous ions – activators of free-radical reaction, inhibitors of hyaluronidase and collagen synthesis stimulators, thus suppressing reverse reaction aimed at the synthesis of connective tissue components. Polytropic properties of bovhyaluronidase azoximer are realized

in pronounced antifibrotic effect experimentally proved by biochemical, histological and electron microscopic studies in pulmonary fibrosis model.

Bovhyaluronidase azoximer regulates (increases or decreases depending on the initial level) inflammatory mediators synthesis (interleukin-1 and tumor necrosis factor alpha), is able to weaken the progress of acute phase of inflammation, enhance humoral immune response and the resistance of the body to infection. The specified properties let to use bovhyaluronidase azoximer during and after surgical treatment for prevention of coarse cicatrization and adhesion. Application of therapeutic doses of bovhyaluronidase azoximer during and after surgical treatment does not cause worsening of postoperative period course or infectious process progress; does not delay bone tissue repair.

Bovhyaluronidase azoximer when coadministered subcutaneously and intravenously increases medicinal products absorption, accelerates anesthesia at local anesthetics administration.

Bovhyaluronidase azoximer is almost a non-toxic compound, does not influence normal immune system functioning, does not influence reproductive function of male and female rats, pre – and postnatal development of offspring, does not possess mutagenic and cancerogenic activity. Experiments results showed that irritating and allergizing properties of hyaluronidase enzyme are decreased in bovhyaluronidase azoximer. Therapeutic doses of bovhyaluronidase azoximer are well tolerated by patients.

Pharmacokinetics

Following parenteral administration bovhyaluronidase azoximer rapidly absorbs to systemic circulation and reaches its peak serum concentration in 20 – 25 min, and is characterized by high body distribution. Distribution half-life – about 0.5 h, elimination half-life ($T_{1/2}$) - 36 hours following intramuscular administration and 45 hours following subcutaneous administration. Apparent volume of distribution – 0.43 l/kg. Conjugation does not decrease high bioavailability of the enzyme – bioavailability is NLT 90 %.

Active substance penetrates all organs and tissues, including blood-brain and ophthalmic barriers.

In organism hyaluronidase is exposed to hydrolysis and the carrier disintegrates into low-molecular compounds (oligomers) which are excreted mainly via the kidneys in two phases. During the first day 45 – 50 % is excreted via the kidneys, NMT 3 % - via faeces. Then elimination rate decreases, the product is eliminated completely by day 4 – 5.

INDICATIONS

Adults as a part of combination therapy for treatment and prevention of diseases accompanied by connective tissue hyperplasia.

In gynecology: treatment and prevention of adhesive process in lesser pelvis during inflammatory diseases of internal genital organs, including tubo-peritoneal infertility, intrauterine synechiae, chronic endometritis;

In urology: treatment of chronic prostatitis, interstitial cystitis;

In surgery: treatment and prevention of adhesive process after operative treatment of abdominal cavity organs; hypertrophic scars after traumas, burns, surgery, pyoderma; nonhealing wounds;

In dermatovenerology and cosmetology: treatment of localized scleroderma, keloid, hypertrophic scars, scars forming after pyoderma, traumas, burns, surgery.

In pulmonology and phthisiology: treatment of pneumosclerosis, fibrosing alveolitis, tuberculosis (fibro-cavity, infiltrative, tuberculoma);

In orthopedy: treatment of joint contracture, arthrosis, Marie-Striinipell disease, hematomas;

For bioavailability increase: in case of co-administration with anti-infective drugs in urology, gynecology, surgery, dermatovenerology, pulmonology, for potentiation of local anesthetics.

CONTRAINDICATIONS

Hypersensitivity to medicinal products on the basis of hyaluronidase, acute infectious diseases, pulmonary hemorrhage and hemoptysis, recent vitreous hemorrhage, malignant neoplasms, acute renal failure, age under 18 years (no clinical study data available).

WITH CAUTION

Chronic liver failure (administer not more than once per week).

PREGNANCY AND LACTATION

Longidaze® is contraindicated to pregnant and breast-feeding women.

POSODOLOGY AND METHOD OF ADMINISTRATION

Longidaze® is administered subcutaneously (near the affected area or under scarred tissue) or intramuscularly at the dose of 3000 IU as a course of 5 – 25 injections (depending on the disease) with an interval between injections of 3 – 10 days.

Doctor chooses the route of administration depending on the diagnosis, disease severity, clinical progression, patient's age. If necessary, retreatment in 2 – 3 months is recommended.

In case of treatment of diseases accompanied by severe chronic productive process in connective tissue, supportive treatment with Longidaze® 3000 IU with intervals between injections of 10 – 14 days is recommended after standard treatment course.

To increase bioavailability of medicinal and diagnostic agents intramuscular or subcutaneous pretreatment with the dose of 1500 IU, 10 – 15 minutes prior to the main dose, with administration to the same site as the main product is recommended.

Dilution:

1. Dissolve the contents of Longidaze® 3000 IU ampoule or bottle in 1.0 – 2.0 ml of procaine solution (0.25 % or 0.5 %). In case of intolerance to procaine dissolve Longidaze® in the same volume of 0.9 % sodium chloride solution for injection or water for injection.

2. In case the product is administered for bioavailability increase dissolve the contents of Longidaze® 3000 IU ampoule or bottle in 2.0 ml, and the contents of Longidaze® 1500 IU ampoule or bottle in 1.0 ml of 0.9 % sodium chloride solution for injection.

Introduce the solvent to a bottle or ampoule slowly, allow to stand for 2 – 3 minutes, mix carefully without shaking to prevent protein foaming.

The prepared solution for parenteral use is non-storable.

Do not inject intravenously!

Recommended schemes for prevention and treatment

- **For prevention** of peritoneal adhesions and coarse cicatrization after surgical treatment of abdominal cavity and lesser pelvis organs, make a course of 5 intramuscular injections in the dose of 3000 IE, 1 injection every third day. If necessary, proceed Longidaze® administration as a course of up to 10 injections, 1 injection every 5 days.
- **For treatment.**

in gynecology:

- of adhesive process in lesser pelvis during inflammatory diseases of internal genital organs, - 3000 IU intramuscularly, 1 injection every 3 – 5 days, a course of 10 – 15 injections.

- tubo-peritoneal infertility, - 3000 IU intramuscularly, a course of up to 15 injections: the first 5 injections: 1 injection every 3 days, afterwards – 1 injection every 5 days;

in urology:

- chronic prostatitis, - 3000 IU intramuscularly, 1 injection every 5 days, a course of 10 – 15 injections;
- interstitial cystitis, - 3000 IU intramuscularly, 1 injection every 5 days, a course of up to 10 injections;

in surgery:

- peritoneal adhesions after operative treatment of abdominal cavity organs, - 3000 IU intramuscularly, 1 injection every 3 – 5 days, a course of 10 – 15 injections;
- nonhealing wounds, - 3000 IU intramuscularly, 1 injection every 5 days, a course of 5 – 10 injections;

in dermatovenerology, cosmetology:

- localized scleroderma, - 3000 – 4500 IU intramuscularly, 1 injection every 3 – 5 days, a course of up to 20 injections. Choose the dosage and course individually, depending on clinical progression, stage, disease localization and patient's individual peculiarities;
- keloid, hypertrophic scars, scars forming after pyoderma, burns, surgery, traumas: intrascar or subcutaneous injection near the affected area, - 3000 – 4500 IU, 1 injection every 3 days, a course of up to 15 injections. Doctor chooses Longidaze® dilution volume depending on the number of administration sites. In necessary, proceed the course by the scheme 1 injection every 5 days, up to 25 injections. Depending on the affected skin area and scarring time it is possible to interchange subcutaneous and intramuscular injections, 1 injection of 3000 IU every 5 days, a course of up to 20 injections.

in pulmonology and phthisiology:

- treatment of pneumosclerosis, - 3000 IU intramuscularly, 1 injection every 5 days, a course of 10 injections;
- fibrosing alveolitis, 3000 IU intramuscularly, 1 injection every 5 days, a course of 15 injections, afterwards – supportive therapy, 1 injection every 10 days, a course of up to 25 injections;
- tuberculosis. - 3000 IU intramuscularly, 1 injection every 5 days, a course of up to 25 injections; depending on clinical performance and disease severity long-term therapy is possible (6 months – 1 year in the dose of 3000 IU, 1 injection every 10 days);

in orthopedy:

- joint contractures, - 3000 IU subcutaneously near the affected area, 1 injection every 3 days, a course of 5 – 15 injections;
- arthrosis, Marie-Striinipell disease, - 3000 IU subcutaneously near the affected area, 1 injection every 3 days, a course of up to 15 injections, if necessary, proceed the treatment by 1 injection every 5 days. Doctor chooses the duration of supportive therapy depending on the disease severity;
- hematomas; - 3000 IU subcutaneously near the affected area, 1 injection every 3 days, a course of up to 5 injections;

For bioavailability increase: in case of subcutaneous or intramuscular co-administration with diagnostic or medicinal products (antibiotics, chemotherapeutic agents, anesthetics, etc.) pretreat Longidaze® 10 – 15 minutes prior the main product at the dose of 1500 IU and by the same method and to the same site as the main product.

ADVERSE EVENTS

Common ($\geq 1/100$ to $< 1/10$) – painfulness at injection site. Uncommon ($\geq 1/1,000$ to $< 1/100$) –

injection site reaction such as skin redness, itching and edema. All local reactions resolve themselves in 48 – 72 hours. Very rare (< 1/10000) – allergic reactions.

OVERDOSE

Overdose symptoms can be expressed in chill, temperature increase, dizziness, hypotension. The medicinal product is discontinued and symptomatic therapy is prescribed.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Bovhyaluronidase azoximer can be combined with antibiotics, antiviral, antifungal drugs, bronchial spasmolytics. When administered in combination with other medicinal product (antibiotics, local anesthetics, diuretics) bovhyaluronidase azoximer increases their bioavailability and enhances their effect. In case of co-administration with high doses of salicylates, cortisone, adrenocorticotrophic hormone (ACTH), estrogens or antihistaminic drugs bovhyaluronidase azoximer enzymatic activity can decrease.

Do not co-administer bovhyaluronidase azoximer with medicinal products containing furosemide, benzodiazepines, phenytoin.

SPECIAL WARNINGS

When required Longidaze[®] can be discontinued at once, without gradual dose decrease.

If medicinal product dose is missed continue its further administration as usual, according to the present Instruction on Use or to the doctor's recommendations. A patient should not administer double dose to compensate the missed doses.

Tell Your doctor about all the medicinal products You take before treatment initiation. Consult Your doctor before use. Read Instruction on Use and keep it.

Follow the Instruction on Use strictly. If You have any questions, consult Your doctor or pharmacist.

In case of chronic liver failure the medicinal product is prescribed to be administered not more often than once per week.

If allergic reaction develops discontinue the medicinal product Longidaze[®] and consult Your doctor.

Do not use the product in case of visual signs of its invalidity (package defect, change of powder color).

Do not inject medicinal product Longidaze[®] to acute infection site because of the danger of localized infection spread.

INFLUENCE ON ABILITY TO DRIVE AND USE MECHANISMS

Longidaze[®] administration does not influence the ability to perform hazardous activities requiring increased concentration of attention and quick psychomotor reactions (including driving, using moving mechanisms).

PHARMACEUTICAL FORM:

Lyophilizate for solution for injection.

15 mg (for 1500 IU dose) or 20 mg (for 3000 IU dose) per 3 ml hydrolytic class 1 amber glass ampoules or bottles. 5 ampoules or bottles with the product per polyvinylchloride film blister. One blister together with Instruction on Use per carton pack. Or 5 ampoules or bottles together with Instruction on Use per carton pack with carton insert element.

STORAGE CONDITIONS

In a place protected from light.
Keep out of reach of children.

SHELF LIFE

2 years. Do not use after the expiry date.

PHARMACY PURCHASING TERMS

On prescription.

**MANUFACTURER/LEGAL BODY TO WHOM THE MARKETING AUTHORIZATION
WAS GRANTED**

Manufacturer and Marketing Authorization Holder:

NPO Petrovax Pharm, LLC

Legal address / Address of manufacture/ Address for customers' complaints:

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