Stamp: Ministry of Health of Russia; ЛС-000764-220818; AGREED

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

PATIENT INFORMATION LEAFLET

OF THE DRUG PRODUCT LONGIDAZA®

Registration number: ЛС-000764

Trade name: Longidaza®

**International nonproprietary name:** Bovhyaluronidase Azoximer

(bovhyaluronidasum azoximerum)

**Chemical name:** bovine hyaluronidase conjugate with N-oxide copolymer of 1,4-ethylenepiperazine and (N-carboxymethyl)-1,4-ethylene-piperazinium bromide

**Pharmaceutical form:** lyophilized for solution for injection

**Composition for 1 vial:**

Active ingredient: Bovhyaluronidase azoximer (Longidaza®) 1500 IU or 3000 IU Excipient: mannitol up to 15 mg (for 1500 IU strength) or up to 20 mg (for 3000 IU strength)

**Description:** white hygroscopic porous mass with or without yellowish or beige shade.

**Pharmacotherapeutic group: immunomodulatory agent:** enzyme product

**ATC code:** V03 АХ

Pharmacological proprieties

Pharmacodynamics:

Bovhyaluronidase azoximer represents a conjugate of proteolytic enzyme hyaluronidase with high-molecular carrier of N-oxide poly-1,4-ethylenepiperazine derivative group. Bovhyaluronidase azoximer is characterized by a range of pharmacological properties typical of medicinal products with hyaluronidase activity. A specific substrate for hyaluronidase is glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate) - the cementing substance of the connective tissue. As a result of hydrolysis (depolymerization), the viscosity of glycosaminoglycans, ability to bind water and metal ions decreases. As a result, the permeability of tissues increases, their trophism improves, edema decreases, hematomas resolve, the elasticity of scarred areas increases, contractures and adhesions are eliminated, joint mobility increases. The effect is most pronounced in the initial stages of the pathological process.

The clinical effect of Bovhyaluronidase azoximer is significantly higher than the effect of native hyaluronidase. Conjugation increases the resistance of the enzyme to the action of temperature and inhibitors, increases its activity and leads to prolonged action. The enzymatic activity of Bovhyaluronidase azoximer persists when heated at 37 °C for 20 days, while native hyaluronidase under the same conditions loses its activity during the day. Bovhyaluronidase azoximer retains the pharmacological properties of a carrier with chelating, antioxidant, anti-inflammatory and immunomodulating activity. Bovhyaluronidase azoximer is able to bind iron ions released during the hydrolysis of glycosaminoglycans – activators of free radical reactions, inhibitors of hyaluronidase and stimulators of collagen synthesis, 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 antifibrotic effect, experimentally proved by biochemical, histological and electron microscopic studies on the model of pneumofibrosis.

Bovhyaluronidase azoximer regulates (increases or decreases, depending on the initial level) the synthesis of inflammatory mediators (interleukin-1 and tumor necrosis factor-alpha), can weaken the course of the acute phase of inflammation and increase the body's antibody responsiveness and resistance to infection. These properties enable the use of Bovhyaluronidase azoximer during and after a surgery to prevent rough scarring and adhesive process. The use of Bovhyaluronidase azoximer in therapeutic doses during or after surgical treatment does not cause a deterioration in the course of the postoperative period or the progression of the infectious process. It does not slow down bone repair. Bovhyaluronidase azoximer, when administered in a combined way (subcutaneously, intramuscularly) increases the bioavailability of drugs, enhances analgesia of locally administered anesthetics.

Bovhyaluronidase azoximer is referred to virtually non-toxic compounds, does not disturb normal immune system functioning, does not have any impact on the reproductive function male and female rats, pre- and postnatal development, does not have mutagenic or cancerogenic action. It has been experimentally proven that the irritant and allergenic properties of the enzyme hyaluronidase are reduced in the Bovhyaluronidase azoximer. Bovhyaluronidase azoximer in therapeutic doses is well tolerated by patients.

**Pharmacokinetics:**

Following parenteral administration, Bovhyaluronidase azoximer is rapidly absorbed into systemic blood and peak concentration is achieved in blood after 20 - 25 minutes, it is characterized by high distribution rate in the body. Half-life is about 0.5 h, half-life (T½) following intramuscular administration is 36 h, following subcutaneous administration - about 45 h. The apparent volume of distribution is 0.43 l/kg. The conjugation does not reduce high bioavailability of the enzyme - bioavailability is not less than 90 %.

The active ingredient has been shown to penetrate into all organs and tissues, pass through hemato-encephalic and ophthalmic barriers.

Hyaluronidase is subject to hydrolysis in the body, and the carrier splits into low-molecular compounds (oligomers) excreted mainly through kidneys in two phases. During the first two days 45 - 50 % is excreted in the urine, not more than 3 % - in faeces. After that the rate of elimination is decreased, by Day 4 - 5 the drug is excreted completely.

Therapeutic indications:

In adults as part of combined therapy and prevention of connective tissue hyperplasia diseases:

in gynecology - treatment and prevention of adhesion in the lesser pelvis in inflammatory diseases of the internal genital organs including tuboperitoneal infertility, intrauterine synechia, chronic endometritis;

in urology - treatment of chronic prostatitis, interstitial cystitis;

in surgery - treatment and prevention of adhesions after surgical interventions in the abdominal organs and long-term non-healing wounds;

in dermatovenereology and cosmetology — treatment of limited scleroderma, non-infectious onychodystrophy, keloid, hypertrophic scars after pyoderma, injuries, burns, surgeries, vulgar acne stage II-IV with scar deformities (postacne);

in pulmonology and phthisiology - treatment of pneumosclerosis, fibrosing alveolitis, tuberculosis (fibrocavernous, infiltrative, tuberculoma);

in rheumatology - treatment of joint contracture including Dupuytren contracture and flexial tendogenic contractures of the hand, arthrosis, ankylosing spondyloarthritis, hematoma;

to increase bioavailability - in combined use of antibacterial drugs in urology, gynecology, surgery, dermatovenerology, pulmonology, to enhance the action of local anesthetics.

Posology and Method of administration

Longidaze® used: subcutaneously, intramuscularly, topically.

Methods of use are chosen by the doctor depending on the diagnosis, severity and clinical course of the disease.

Solution preparation:

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

2. When applied using photophoresis for onychodystrophy treatment, the content of the vial of Longidaza® 3000 IU is diluted in 0.5 ml of distilled water, dissolved for 3-4 minutes, apply 1 drop (about 300 IU of Longidaze®) to distal phalanges of the fingers.

3. For photophoresis or ultrafonophoresis in the treatment of vulgar acne 1 vial of Longidaza® 3000 IU is diluted in 2-5 ml of gel for ultrasound exposure (“Mediagel-T”) and applied to the lesion focus.

4. For drug administration using ultrasound in the treatment of contractures, the content of the vial with Longidaza 3000 IU are dissolved in 1.0 ml of saline, mixed with 5-7 g of Vaseline and applied to the scar area.

5. For increased bioavailability, the content of the vial of Longidaza® 3000 IU is dissolved in 2.0 ml of 0,9% sodium chloride solution for injection.

Inject the solvent in the vial slowly, hold for 2-3 minutes, stir gently, without shaking, so as not to foam the protein.

**The prepared solution for parenteral administration should not be stored.**

**Do not administer intravenously!**

Contraindications:

- hypersensitivity to bovhyaluronidase azoximer and to any of the excipients;

- acute infectious diseases without concomitant use of antimicrobials;

- pneumorrhagia and haemoptysis;

- recent vitreous haemorrhage;

- malignant neoplasms;

- acute renal failure;

- age below 18 years (no data on efficacy and safety are available);

- pregnancy and lactation.

Contraindications during administration of the drug product by physiotherapeutic procedures:

- Hypersensitivity to laser radiation and ultrasonic exposure.

- Photodermatitis.

- Use of steroid hormonal agents by a patient.

- Joint inflammation.

- Somatic diseases for which it is contraindicated to conduct physiotherapeutic procedures.

With caution:

- chronic renal failure (administered not more than once a week).

**Pregnancy and lactation:**

Longidaza® is contraindicated to pregnant and lactating women.

Posology and method of administration:

Longidaza® is used: subcutaneously, intramuscularly, topically.

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

***Solution preparation:***

1. For subcutaneous or intramuscular injection dissolve the content of a bottle of the drug product Longidaza® 3000 IU in 1.0 - 2.0 ml of 0.5 % procaine (novocaine) solution. In case of procaine (novocaine) intolerability, dissolve Longidaza® in the same volume of 0.9 % sodium chloride for injection or water for injection.

For subcutaneous or intramuscular injection dissolve the content of a bottle of the drug product Longidaza® 1500 IU in 1.0 - 2.0 ml of 0.5 % procaine (novocaine) solution. In case of procaine (novocaine) intolerability, dissolve Longidaza® in the same volume of 0.9 % sodium chloride for injection or water for injection.

For subcutaneous or intramuscular injection of Longidaza® in the dosage 4500 IU the contents of a bottle of Longidaza® 3000 IU are dissolved in 1.0-2.0 ml of 0.5% procaine (novocaine) solution, the contents of the bottle of Longidaza® 1500 IU are dissolved in 1.0-2.0 ml 0.5% procaine (novocaine) solution. Both obtained solutions are taken alternatively in a syringe of at least 5 ml.

2. For use of photophoresis for treatment of onychodystrophy, dilute the content of a vial of the drug product Longidaza® 3000 IU in 0.5 ml of distilled water, dissolve for 3 - 4 minutes, apply 1 drop (about 300 IU of the drug product Longidaza®) on phalangettes.

3. For performance of photophoresis or ultraphonophoresis for treatment of acne vulgaris, dilute 1 vial of the drug product Longidaza® 3000 IU in 2 - 5 ml of a gel for ultrasound exposure (Mediagel-T) and apply on lesion.

4. For administration of the drug product using ultrasound for treatment of contractures, dissolve content of a vial with Longidaza 3000 IU in 1.0 ml of normal saline, mix with 5 - 7 g of vaseline and apply on the area of a scar.

5. For use in order to increase bioavailability of the drug product Longidaza® 3000 IU, dissolve content of a vial in 2.0 ml, for strength 1500 IU - in 1.0 ml of 0.9 % sodium chloride for injection.

Introduce the solvent into a vial slowly, allow to stand for 2 - 3 minutes, cautiously mix, do not shake in order to avoid protein foaming.

**The prepared solution for parenteral administration is not subjected to storage.**

**Not for intravenous injection!**

**The recommended regimens of prevention and treatment**

о **Recommended regimens of prevention and treatment**

* **For the prevention** of adhesions and coarse scarring after surgical interventions in the abdominal and pelvic organs: 3000 IU intramuscularly once every 3 days by course of 5 injections. If necessary, the use of Longidaza® can be continued by general course of up to 10 injections when administered once every 5 days.
* ***For treatment***

**in gynecology:**

- adhesions in the lesser pelvis in inflammatory diseases of the internal genital organs: 3000 IU intramuscularly once every 3-5 days by course of 10-15 injections;

tuboperitoneal infertility 3000 IU intramuscularly, by general course of up to 15 injections: the first 5 injections once every 3 days, then once every 5 days;

**in urology:**

chronic prostatitis: 3000 IU intramuscularly once every 5 days by course of 10-15 injections;

- interstitial cystitis: 3000 IU intramuscularly once every 5 days by course of up to 10 injections;

**in surgery:**

- adhesions after surgical interventions in the abdominal organs: 3000 IU intramuscularly once every 3-5 days by course of 10 to 15 injections;

- long-term non-healing wounds: 3000 IU intramuscularly once every 5 days by course of 5-10 injections;

**in dermatovenereology, cosmetology:**

limited scleroderma: intramuscularly once every 3-5 days by 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;

- non-infectious onychodystrophy: apply 1 drop of prepared solution (approximately 300 IU of the Longidaza®) to the area of projection of the posterior nail fold, without time interval exposure to low-intensity infrared laser radiation with pulse frequency 80-1500 Hz, pulse duration 110-160 ns, at pulse power 4-6 W/pulse. Photophoresis is carried out according to the contact stable method, 1 minute on the field, the total exposure time is up to 10 minutes with isolated lesions of the nails of hands or feet and up to 20 minutes with combined lesions nail of hands or feet. Course is 15 procedures, daily;

keloid, hypertrophic and forming scars after pyoderma, burns, surgeries, injuries: intrascar or subcutaneous near the lesion site administration once every 3 days, a course of up to 15 injections. The volume of dilution of the drug Longidaze® is chosen by the doctor depending on the number of points of administration. If necessary, the course can be continued according to the scheme once every 5 days to 25 injections. Depending on the area of skin lesions, the limitation of scar formation, it is possible to alternate subcutaneous and intramuscular administration once every 5 days by course of up to 20 injections;

- vulgar acne stage II-IV with scar deformity (postacne):

3000 IU intramuscularly, 2 injections per week for up to 10 injections.

Longidaza® can be administered using photophoresis or ultrafonophoresis daily, 5 days a week - 3 weeks, 15 procedures per course. The compounded solution is applied to the lesion area and without time interval exposure to low-intensity infrared laser radiation with pulse frequency 80-1500 Hz or ultrasound at 880 kHz -1 MHz in continuous or pulse mode is carried out. When localization of the lesion focus on the face, the intensity of ultrasound exposure is 0.2-0.4 W/cm2. Depending on the area of impact, a small emitter is used - 1 cm2, average - 2 cm2 or large - 4 cm2. Procedure of exposure is contact labile. The total impact area should not exceed 50 cm2. Total exposure time is 5 minutes.

**in Pulmonology and Phthisiology:**

- pneumosclerosis: 3000 IU intramuscularly once every 5 days by course of 10 injections;

- fibrosing alveolitis: 3000 IU intramuscularly once every 5 days by course of 15 injections, further maintenance therapy once every 10 days by general course of up to 25 injections;

- Tuberculosis: 3000 IU intramuscularly once every 5 days by course of up to 25 injections. Depending on the clinical picture and severity of the disease course, long-term therapy is possible (from 6 months to 1 year, once every 10 days);

**in rheumatology:**

- contractures of joints including Dupuytren contractures and flexural tendogenic contractures of the hand, 3000 IU subcutaneously into the area of contracture once a day, daily for 5 days with a further break for two days, by course of up to 15 injections. Repeated course - after 1.5 months.

In the case of local reactions to the injection of Longidaza® can be administered by phonophoresis on the area of contracture, every other day, 3 times a week, by course of up to 12 procedures. The compounded solution is applied to the scar area, exposure by an ultrasonic sensor according to the labile technique at the intensity of ultrasound 0.2 W/cm2, in a continuous mode is performed, the duration of the procedure is 10 minutes. Repeated course - after 1.5 months;

- arthrosis, ankylosing spondyloarthritis: 3000 IU subcutaneously near the lesion site once every 3 days by course of up to 15 injections; if necessary, treatment can be continued with injections once in 5 days. The duration of maintenance therapy is chosen by the doctor, depending on the disease severity;

- hematomas: 3000 IU subcutaneously near the lesion site once every 3 days by course of up to 5 injections.

**Undesirable effects:**

Classification of undesirable effects by system organ classes with indication of their frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000), including individual reports, frequency unknown (frequency cannot be evaluated based on available data).

Skin and subcutaneous tissue disorders: uncommon - erythema, pruritus and edema in injection/application site. All local reactions resolve spontaneously after 48 - 72 hours.

General disorders and administration site conditions: common - painful injection site.

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

Investigations: very rare - increased body temperature is possible.

If you notice any adverse effects not listed in this instruction, inform your doctor.

Overdose:

Overdose symptoms may be manifested by chills, increased temperature, dizziness, decreased blood pressure. The drug product is discontinued and symptomatic therapy is administered.

Interactions with other medicinal products:

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

When used in combination with other drugs (antibiotics, local anesthetics, diuretics) Longidaza® increases bioavailability and enhances their effect. In combined use combined with heparin, large doses of non-steroidal anti-inflammatory drugs (NSAIDs), cortisone, adrenocorticotropic hormone (ACTH), estrogens or antihistamines may be reduced enzymatic activity of Longidaza®.

Do not use Longidaza® simultaneously with furosemide, benzodiazepines, phenytoin and adrenaline.

Special warnings:

If an allergic reaction develops, the drug product Longidaza® should be discontinued and a physician should be consulted.

If you need to discontinue Longidaza®, it should be made immediately, without a gradual dose decrease.

If you miss a successive dose of the drug product, its subsequent use should be carried out as usual, as indicated in this leaflet or recommended by a physician. The patient should not administer a double dose in order to compensate the missed doses.

Do not use the drug in the presence of visual signs of its unsuitability (packaging defect, discoloration of the powder).

Do not administer Longidaza® to the area of acute infectious inflammation due to danger of localized infection spread.

For treatment of diseases accompanied with severe chronic productive process in connective tissue, after a standard course, a long-term supportive therapy with Longidaza® 3000 IU with intervals between injections of 10 - 14 days is recommended after a standard course.

Effects on ability to drive and use machines:

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

Presentation:

Lyophilizate for preparation of the solution for injection.

20 mg in 3 ml amber glass vials of hydrolytic grade 1. 5 vials in polyvinyl chloride film blister. One blister package with instructions for use is placed in a carton pack.

Shelf life:

2 years. Do not use after the expiry date.

Storage conditions:

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

Keep out of the reach of children.

Pharmacy purchasing terms:

Prescription only.

Manufacturer/Legal entity in whose name the marketing authorization is issued:

Manufacturer and Marketing Authorization Holder:

NPO Petrovax Pharm LLC

Legal address / Manufacturing address / Address for filing consumer claims:

1 Sosnovaya ul., Pokrov village, Podolsk, Moscow Region, 142143, Russia, tel./fax: +7 495 926-21-07, e-mail: info@petrovax.ru;

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 tel.: +7 (495) 730-75-45, 8 (800) 234-44-80, e-mail:ru.

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| Representative | */signature/*  |  |
| NPO Petrovax Pharm LLC | M.S. Makoeva |

**Round seal**: NPO Petrovax Pharm LLC. Regulatory affairs department. Moscow region. OGRN 1037700012745

Stamp: Ministry of Health of Russia; ЛС-000764-220818; AGREED

Bound and numbered and sealed 11 sheets.

Representative of NPO Petrovax Pharm LLC, T.V. Pankratova

/signature/

17.07.2018

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