/Stamp: *MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION*
** LSR-002940/07*
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APPROVED/

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

MEDICINAL PRODUCT LABEL

LONGIDAZA®

Registration number:

Trade name: Longidaza®

International Nonproprietary Name: Bovhyaluronidase azoximer

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

Dosage form: vaginal and rectal suppositories

Composition per suppository:

Active ingredient: Bovhyaluronidase azoximer (Longidaza®) - 3000 IU Excipient: cocoa seed oil (cocoa butter) - to obtain a suppository weighing 1.3 g

Appearance: light yellow torpedo-shaped suppositories, light yellow in color with mild specific cocoa butter odor; mottled coloration is permitted. On the section, the presence of an air stem or funnel-like recession is permitted.

Pharmacotherapeutic group: enzyme agent

ATC code: V03AX

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Longidaza® drug product has prolonged hyaluronidase (enzymatic) potency, chelating, antioxidant, immunomodulatory, and moderate anti-inflammatory properties. The prolongation of the enzyme's action is achieved by covalently binding the enzyme to a physiologically active polymeric carrier (azoximer). Longidaza® drug product exhibits antifibrotic properties, attenuates the acute phase of inflammation, regulates (increases or decreases depending on the initial level) synthesis of inflammatory mediators (interleukin-1 and alpha tumor necrosis factor), increases humoral immune response and resistance to infection.

Pronounced antifibrotic properties of Longidaza® drug product are provided by conjugation of hyaluronidase with the carrier, which significantly increases the robustness of the enzyme to denaturing effects and the action of inhibitors: the enzymatic potency of Longidaza® drug product is maintained when heated to 37 °C for 20 days, while native hyaluronidase in the same conditions

loses its potency within a day. Longidaza® drug product provides simultaneous local presence of hyaluronidase enzyme and a carrier, capable of binding enzyme inhibitors and stimulators of collagen synthesis (iron ions, copper ions, heparin, etc.) released during hydrolysis of matrix components. Due to the above properties, Longidaza® drug product not only has the ability to depolymerize the matrix of connective tissue in fibrous granulomatous masses, but also to inhibit the reverse regulatory reaction aimed at the synthesis of connective tissue components.

The specific substrate of testicular hyaluronidase is glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulphate, chondroitin-6-sulphate), which form the matrix of connective tissue. As a result of depolymerization (breaking the bond between C_1 acetylglucosamine and C_4 glucuronic or induronic acids) glycosaminoglycans change their basic properties: viscosity decreases, the ability to bind water and metal ions decreases, the permeability of tissue barriers temporarily increases, fluid movement in the intercellular space is facilitated, and the elasticity of connective tissue increases, which is demonstrated by a reduction in tissue swelling, flattening of scars, increased joint movement volume, reduction in contractures and prevention of their formation, and reduction in adhesive process. Biochemical, immunological, histological, and electron microscopic studies have proved that Longidaza® drug product does not damage the normal connective tissue, but causes destruction of connective tissue altered in composition and structure in the fibrosis area.

Longidaza® drug product has no mutagenic, embryotoxic, teratogenic or carcinogenic effects.

Longidaza® drug product is well tolerated by patients and no local or general allergic reactions have been observed.

The use of Longidaza® drug product in therapeutic doses during or after surgical treatment does not cause deterioration of the course of postoperative period or progression of infection; it does not delay bone regeneration.

Pharmacokinetics

Experimental study of pharmacokinetics has allowed to establish that during rectal administration Longidaza® drug product is characterized by high speed of distribution in the body, is well absorbed into the systemic bloodstream and reaches maximum concentration in the blood after 1 hour. The distribution half-life time is about 0.5 hour, the elimination half-life is from 42 to 84 hours. It is mostly excreted by the kidneys.

The drug product penetrates all organs and tissues, including the blood-brain barrier and the haemato-ophthalmic barrier. No tissue cumulation has been established.

The bioavailability of Longidaza® drug product by rectal administration is high: about 90%.

INDICATIONS FOR USE

Adults and adolescents over 12 years of age, as monotherapy and in the treatment of diseases accompanied by connective tissue hyperplasia, including inflammatory conditions:

- in urology: chronic prostatitis (including relapse prevention), interstitial cystitis, urethral and renal duct strictures, Peyronie's disease, initial stage of benign prostatic hyperplasia, prevention of scarring and stricture formation after surgical interventions on the urethra, bladder, and renal ducts;
- in gynecology: adhesive process (prevention and treatment) in the pelvis in chronic inflammatory diseases of the internal genitals, after gynecologic manipulations, including artificial abortions, previous pelvic surgery; intrauterine synechias, tuboperitoneal sterility, chronic endomyometritis;
- in dermatovenereology: limited scleroderma, prevention of fibrotic complications of sexually transmitted infections;
- in surgery: -treatment and prevention of adhesive process after surgical interventions on the abdominal organs and long-term non-healing wounds;
- in pulmonology and phthisiology: pneumofibrosis, siderosis, tuberculosis (cavernofibrosis, infiltrative, tuberculoma), interstitial pneumonia, fibrosing alveolitis, pleurisy;
- to increase the bioavailability of antibiotic therapy in urology, gynaecology, dermatovenerology, surgery, pulmonology, etc.

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or any other component of the drug product;
- Pneumorrhagia, hemoptysis;
- fresh hemorrhage in vitreous humor;
- acute renal failure;
- Children under 12 years of age (no data from clinical studies are available);
- malignant neoplasms;
- pregnancy, breastfeeding period.

WITH CAUTION

Use with caution not more than once a week in patients with chronic renal failure, history of pulmonary hemorrhage.

USE DURING PREGNANCY AND BREASTFEEDING

Use during pregnancy is contraindicated (no data on the safety of the medicinal product in pregnancy).

According to the available preclinical data, administration of the drug product in doses 10 times higher than equitherapeutic ones has no negative effect on lactation and offspring development. The results of experimental studies provide no direct evidence for the absence of Longidaza® drug product excretion with milk in animals. Breastfeeding must be stopped on initiation of treatment with the drug product during lactation.

POSOLOGY AND METHOD OF ADMINISTRATION

Longidaza® suppositories 3000 IU are recommended for **rectal or vaginal** use q.d. at night with a course of 10 to 20 administrations.

For adolescents aged 12 to 18, suppositories are only rectally administered.

For adults and adolescents over 12 years of age rectally: 1 suppository once a day after bowel evacuation.

For adults vaginally: 1 suppository once a day (at night) into the vagina in a supine position.

The route of administration is adjusted according to the severity, stage, and duration of the disease: Longidaza® drug product is administered on alternate days or at 2-3 day intervals. Recommended regimen and doses:

- in urology: 1 suppository on alternate days (10 suppositories), then every 2-3 days (10 suppositories) for a total of 20 suppositories.
- in gynaecology: rectally or vaginally 1 suppository every 2 days (10 suppositories), followed by supportive therapy if necessary.
- in dermatovenerology: 1 suppository every 1-2 days (10-15 suppositories).
- in surgery: 1 suppository every 2-3 days (10 suppositories).
- in pulmonology and phthisiology: 1 suppository every 2-4 days (10-20 suppositories). If necessary, retreatment with Longidaza® drug product is recommended at the earliest after three months or long-term maintenance therapy with 1 suppository every 5-7 days for 3-4 months.

If there is no improvement during treatment, or if symptoms worsen or new symptoms appear, please consult your doctor. Use the drug product only according to the indications, method of administration, and in those doses as stated in the instruction.

SIDE EFFECTS

The frequency of adverse reactions is classified as follows: very frequent ≥ 10 %; frequent ≥ 1 % and < 10 %; infrequent ≥ 0.1 % and < 1 %; rare ≥ 0.01 % and < 0.1 %; and very rare < 0.001 %.

Very rare: local reactions such as erythema, swelling, perianal pruritus, vaginal pruritus associated with individual sensitivity to drug product components.Tell your doctor, if you experience or side effects that are not mentioned in the package leaflet, or if the said side effects worsen, or if you notice any other side effects that are not mentioned in the package leaflet.

OVERDOSE

Symptoms of overdose may include chills, fever, dizziness, and hypotension. Treatment: drug product withdrawal, symptomatic treatment.

INTERACTION WITH OTHER MEDICINAL PRODUCTS

Longidaza® drug product can be combined with antibiotics, antivirals, antifungals, and bronchodilators. When used in combination with other medicinal products (antibiotics, local anesthetics, diuretics) the possibility of increased bioavailability and potency should be considered. Co-administration with high doses of salicylates, cortisone, adrenocorticotropic hormone (ACTH), estrogens or antihistamines may reduce the enzymatic potency of Longidaza® drug product.

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

If you are using the above or other drug products (including over-the-counter drug products), consult your doctor before using Longidaza® drug product.

SPECIAL WARNINGS

Strictly follow the directions in the package leaflet carefully when taking the medicinal product.

For further information, consult your doctor.

If you experience any adverse reactions, you should stop using Longidaza® drug product and consult your doctor.

When used against a background of worsening foci of infection, it should be administered under the cover of antimicrobials to prevent the spread of infection.

As there may be an unpredictable acceleration of adsorption and increased systemic action, caution should be exercised and the pharmacokinetic characteristics of the medicinal products administered in combination with Longidaza® drug product should be considered.
Do not use the drug product if there are visual signs of its unsuitability (packaging defect, suppository color change).
If the administration of next dose is missed, continue as usual (do not administer a double dose).
If it is necessary to stop taking Longidaza®, the drug product can be stopped immediately, without gradually decreasing the dose.

EFFECTS ON ABILITY TO DRIVE VEHICLES AND OPERATE MACHINERY

The use of Longidaza® drug product does not affect the ability to drive vehicles, operate machinery and perform other types of work requiring high concentration and quick psychomotor reactions.

PRESENTATION

Vaginal and rectal suppositories 3000 IU.
5 suppositories in a polyvinyl chloride blister pack. One, two or four blister packs in a cardboard box, together with the package leaflet.

STORAGE CONDITIONS

Protect from light. Store at a temperature not exceeding 15 °C. Do not freeze. Keep out of the reach of children.

EXPIRY DATE

2 years. Do not use after expiry date.

DISPENSING CONDITIONS

Over the counter.

MANUFACTURER / LEGAL ENTITY IN WHOSE NAME THE MARKETING AUTHORIZATION HAS BEEN ISSUED/ORGANIZATION THAT ACCEPTS CLAIMS FROM CONSUMERS

Marketing Authorization Holder and Manufacturer:

NPO Petrovax Pharm LLC

Legal address/Address for filing consumer claims:

Sosnovaya str., 1, vil. Pokrov, Podolsk, 142143, Moscow region, Russian Federation, tel./fax: +7(495) 926-21-07, e-mail: info@petrovax.ru;

for filing claims:

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

Manufacture / Filling (primary packaging):

10, Zagorievskaya St., Bldg.4, Moscow, 115598, Russian Federation,

Tel./fax: +7 (495) 329-17-18.

1, Sosnovaya st., Pokrov village, Podolsk, 142143, Moscow region, Russia,

Tel./fax: +7 (495) 926-21-07

Secondary (consumer)/commercial packaging/Batch release:

1, Sosnovaya st., Pokrov village, Podolsk, 142143, Moscow region, Russia,

Tel./fax: +7 (495) 926-21-07

Representative of NPO Petrovax Pharm LLC	*/signature/* */Stamp: * LIMITED LIABILITY COMPANY OGRN 1037700012745 * Moscow region*03* NPO Petrovax Pharm/*	Makoeva M.S.

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Totally stitched, numbered, and sealed 8 sheets.
Representative of NPO Petrovax Pharm LLC
Makoeva M. S.
Signature: /*signed*/
28.05.2021

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