MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

PATIENT INFORMATION LEAFLET

for the use of

LONGIDAZA®

Authorization number: ЛСР-002940/07

Trade name: Longidaza®

**International nonproprietary name:** Bovhyaluronidase azoximer (bovhyaluronidasum azoximerum)

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

**Pharmaceutical form:** vaginal and rectal suppositories

**Composition per suppository:**

Active ingredien: Bovhyaluronidase azoximer (Longidasa®) - 3000 IE

Excepient: cocoa seed butter (cocoa oil) - before obtaining of suppository of weight 1.3

**Apperance:** torpedo-shaped, light yellow suppositories with a faint specific odor of cocoa oil, marbling is allowed. An air rod or funnel-shaped recess is allowed on the cut.

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

**ATC code:** V03AX

**PHARMACOLOGICAL PROPERTIES**

Pharmacodynamics

Longidaza® possesses prolonged-action hyaluronidase (enzymatic) activity, chelating, antioxidant, immunomodulating and moderately pronounced anti-inflammatory properties.

The prolongation of the enzyme action is achieved by covalent binding of the enzyme to a physiologically active polymer carrier (azoximer). Longidaza ® exhibits antifibrotic properties, weakens the acute phase of inflammation, regulates (increases or decreases, depending on the initial level) the synthesis of inflammatory mediators (interleukin-1 and tumor necrosis factor-alpha), and increases the humoral immune response and the organism's resistance to infection.

The pronounced antifibrotic properties of Longidaza are provided by conjugation of hyaluronidase with a carrier, which significantly increases the enzyme's resistance to denaturing effects and inhibitors: the enzymatic activity of Longidaza persists when heated to 37°C for 20 days, while native hyaluronidase loses its activity under the same conditions during 1 day. In the Longidaza® preparation, a simultaneous local presence of the hyaluronidase enzyme and a carrier, which is capable of binding the inhibitors of the enzyme and collagen synthesis stimulators (iron, copper ions, heparin, etc.), released upon hydrolysis of the matrix components, is ensured. Due to these properties, Longidaza® possesses not only the ability to depolymerize the matrix of connective tissue in fibro-granulomatous formations, but also to suppress the reverse regulatory reaction, aimed at the synthesis of components of connective tissue.

A specific substrate for testicular hyaluronidase is glycosaminoglycans (hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate), which form the basis of the matrix of connective tissue. As a result of depolymerization (breaking the connection between C1 acetylglucosamine and C4 glucuronic or iduronic acids), glycosaminoglycans change their basic properties: viscosity and the ability to bind water and metal ions decrease, the permeability of tissue barriers temporarily increases, the movement of fluid in the intercellular space is facilitated, and the elasticity of the connective tissue increases that is manifested in a decrease in swelling of the tissue, flattening of scars, an increase in the volume of movement of the joints, a decrease in contractures and prevention of their formation, and a reduction of adhesions. Biochemical, immunological, histological and electron-microscopic studies have proven that Longidaza® does not damage normal connective tissue, but causes the destruction of altered composition and structure of connective tissue in the region of fibrosis.

Longidaza® has no mutagenic, embryotoxic, teratogenic and carcinogenic effects.

The drug is well tolerated by patients~~.~~ No local or general allergic reactions have been noted.

The use of Longidaza® 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.

**Pharmacokinetics**

An experimental study of pharmacokinetics made it possible to establish that with rectal administration, Longidaza® is characterized by a high distribution rate in the body, is well absorbed into the systemic circulation and reaches its maximum concentration in the blood after 1 hour. The half-life is about 0.5 hours, the half-elimination period is from 42 to 84 hours. It is mainly excreted with urine. The drug has been shown to penetrate all organs and tissues, pass through hemato-encephalic and hemato-ophthalmic barriers. Absence of tissue cumulation of the drug has been established.

Bioavailability of the medicinal product Longidaza® at rectal administration is high –>90%.

INDICATIONS FOR USE

For adults and adolescents over 12 years of age as monotherapy and in the composition of complex therapy of conditions, accompanied by connective tissue hyperplasia, including also with underlying inflammatory process:

• in urology: chronic prostatitis, interstitial cystitis, urethral/ureteral structures, Peyronie's disease, initial stage of benign prostatic hyperplasia, prophylaxis of scars and strictures following urethra, bladder, ureters surgeries;

• in gynecology: adhesive process (prophylaxis and treatment) in pelvis in chronic inflammatory diseases of internal genital organs, after surgical procedures, including artifical abortion, past surgical pelvic organs procedure; intrauterine synechiae, tuboperitoneal infertility, chronic endomyometritis;

• in dermatovenerology: localized scleroderma, prophylaxis of fibrous complications of sexually transmitted infections;

• in surgery: treatment and prevention of postoperative adhesions of abdominal organs; long-term non-healing wounds;

• in pulmonology and phthisiology: pneumofibrosis, siderosis, tuberculosis (fibrocavernous, infiltrative, tuberculoma), interstitial pneumonia, fibrous alveolitis, pleuritis;

• to increase bioavailability of antibacterial therapy in urology, gynecology, dermatovenerology, surgery, pulmonology etc.

**CONTRAINDICATIONS**

• hypersensibility to hialuronidase-based medicinal products;

• pneumorrhagia and haemoptysis;

• recent vitreous haemorrhage;

• malignant neoplasms;

• acute renal failure;

• children under 12 years of age (clinical study results are lacking);

• pregnancy and lactation.

**WITH CAUTION**

Use with caution no more than once a week in patients with history of chronic renal impairment, pulmonary hemorrhages.

**USE DURING PREGNANCY AND LACTATION**

The use of the drug Polyoxidonium® is contraindicated for pregnant women and women during breastfeeding (there is no clinical experience of its use in these conditions).

**POSOLOGY AND METHOD OF ADMINISTRATION**

Longidaza® suppositories 3000 IE is recommended for **rectal** or **vaginal use** OD at the bedtime rom 10 to 20 administrations per course.

**For adolescents between 12 and 18 years of age,** suppositories are administered per rectum.

**For adults and adolescents more than 12 years** of age, suppositories are administered per rectum: 1 suppository OD after evacuation of the bowels.

**For female adults,** suppositories are administered vaginally: 1 suppository is introduced into the vagina in the supine position OD (at night).

The administration schedule is adjusted depending on the severity, stage and duration of the disease: Longidaza® is prescribed every other day or with a two- to three-day interruption.

Recommended schedules and dosages:

• in urology: 10 administrations of 1 suppository every other day, then 10 administrations with 2-3-day interval, 20 suppositories per course.

• in gynecology: 10 administrations of 1 suppository per rectum or per vaginum with a 2-day interval, then maintenance therapy is administered as appropriate.

• in dermatovenerology: 10-15 administrations of 1 suppository with 1-2-day interval.

• in surgery: 10 administrations of 1 suppository with a 2-3-day interval.

• in pulmonology and phthisiology: 10-20 administrations of 1 suppository with a 2-4-day interval.

The repeated course of Longidaza® is recommended for at least three months of continued maintenance therapy, 1 suppository OD for 5-7 days for 3-4 months as appropriate.

**ADVERSE EFFECTS**

The rate of adverse reactions is presented across the following classification: very frequent ≥ 10 %; frequent ≥ 1 % and < 10%; infrequent ≥ 0.1 % and < 1 %; rare ≥ 0.01 % and < 0.1 %; very rare < 0.001 %.

Very rare: allergic reactions, local reactions in the form of redness, swelling, itching of the perianal zone, vaginal itching due to individual sensitivity to the components of the drug.

**OVERDOSAGE**

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

**INTERACTION WITH OTHER MEDICINAL PRODUCTS**

The medicinal product Longidaza® may be combined with antimicrobial, antiviral, antifungal, bronchial spasmolytic agents. When administrating in combination with other medicinal products (antimicrobials, local anesthetics, diuretics) it should be noted that their availability and action may increase.

In combined use with high doses of salicylates, cortisone, adrenocorticotropic hormone (ACTH), estrogens or antihistamines, the enzymatic activity of Longidaza® may decrease.

The medicinal product Longidaza® should not be administered along with furosemide-, benzodiazepines-, phenytoin-containing products.

**SPECIAL INSTRUCTIONS**

Keep strictly to the designations given in PIL using the medicinal product.

If You have any questions, please, turn for explanation to Your physician or pharmaceutist.

Discontinue the use of Longidaza®, if allergic reaction develops.

It should be administered under coverage of antimicrobial agents to prevent dissemination of infection using with underlying exacerbations of sites of infection.

When adverse reactions as well as side effects develop, which are not mentioned in PIL, it is necessary to consult Your prescribing physician immediately.

The drug shouldn't be used in case of the presence of visual signs of its unsuitability (packaging defect, discoloration of the suppository).

In case of omission of administration of the next dose, use the product in accordance with its usual regimen (do not administered duplicate dose).

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

**EFFECT ON ABILITY TO DRIVE AND USE MACHINES**

Using the medicinal product Longidaza® does not affect the ability to drive, maintain machinery and conduct other types of work, requiring an increased concentration of attention and speed of psychomotor reactions.

**PRESENTATION**

Vaginal and rectal suppositories, 3000 ME

5 suppositories into polyvinylchloride film blister pack. One, two or four blisters with PIL are placed in a carton pack.

**STORAGE CONDITIONS**

Protected from light at < 15°С. Do not freeze. Keep out of reach of children.

**Shelf life**

2 years. Do not use after expiration date, specified on package.

**DISPENSING CONDITIONS**

Over the counter.

**Legal entity to which the marketing authorization is granted:**

Marketing ***authorization*** holder and manufacturer:

NPO Petrovax Pharm LLC

Legal address / Address for consumers' claims:

Sosnovaya Street 1, Pokrov Village, Podolsk District, Moscow Region, 142143, Russian Federation, tel./fax: (495) 926-21-07, e-mail: info@petrovax.ru; for consumer's claims: tel.: (495) 730-75-45, E-mail: adr@petrovax.ru

Manufacturing/Packing (primary packaging):

Zagoryevskaya Street 10 Building 4, Moscow 115598, Russian Federation, tel./fax: (495) 329-17-18.

Sosnovaya Street 1, Pokrov Village, Podolsk District, Moscow Region, 142143, Russian Federation, tel./fax: (495) 926-21-07.

Secondary (consumer) packaging/ Release quality control:

Sosnovaya Street 1, Pokrov Village, Podolsk District, Moscow Region, 142143, Russian Federation, tel./fax: (495) 926-21-07.

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| General Director | */signature/ /seal/* |  |
| NPO Petrovax Pharm LLC | A.N. Efimov |