LOUTEN®

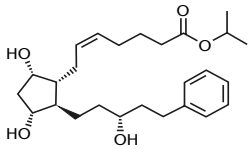
LATANOPROST 0.005%

STERILE OPHTHALMIC EMULSION

Made in Argentina - Rx ONLY

Formula:
Each 100 ml of emulsion contains:
Latanoprost 0.005 g
Médium-Chain triglycerides 1.000 g; Polysorbate 80 0.250 g; Polyethylen glicol 400 0.250 g; Boric acid 1.070 g; Potassium sorbate 0.180 g; Glycerin 0.840 g; Disodium edetate dihydrate 0.010 g; 1N Sodium hydroxide q.s. pH; Purified water q.s. 100 ml.
Each drop of LOUTEN® ophthalmic emulsion contains approximately 1.5 µg of Latanoprost.

Chemical structure:



Latanoprost

$C_{26}H_{40}O_5$
PM: 432,60 g/mol

Thrapeutical action:
Antiglaucoma agent.

Uses:
It is used for reducing the intraocular pressure in patients with open angle glaucoma and eye hypertension.

Pharmacologycal properties:
ATC code: S01EE01.
Pharmacological action:
Latanoprost is a F2α prostaglandin analogous antiglaucoma agent for reducing the intraocular pressure by increasing the outflow of aqueous humor, being its main mechanism of action to increase the uveoscleral outflow. Clinical studies have proved that Latanoprost has causes no significant effects on the production of aqueous humor, and no effect has been observed on the hemato-ocular barrier.
At the clinically doses employed, no pharmacologically significant effects of Latanoprost have been observed on the cardiovascular or respiratory systems.
Pharmacokinetics:
Absorption: Latanoprost is a pro-drug well absorbed through the cornea.
Distribution: The volume of distribution is 0.16 ± 0.02 L/kg. Concentrations of Latanoprost have been measured in the aqueous humor during the first 4 hours and in plasma during the first hour after the ophthalmic topical administration.
Biotransformation: It is an inactive pro-drug of the isopropyl ester type which, but when absorbed by the cornea, it is hydrolyzed by stearases to Latanoprost Acid, the biologically active compound. The portion of Latanoprost reaching the systemic circulation is bio-transformed by the liver to metabolites 1,2 dinor and 1,2,3,4 tetranor by the beta oxidation of the fatty acid.
Half-life ($t_{1/2}$): The elimination of Latanoprost Acid from plasma is rapid (half-life = 17 minutes) and happens after the ophthalmic and intravenous administration as well.
Latency time: Approximately 3 to 4 hours after the administration.
Time to maximum concentration (t_{max}): The peak concentration in the aqueous humor is reached approximately 2 hours after the ophthalmic administration.
Time to maximum effect: This effect is reached after 8 to 12 hours after the ophthalmic topical administration, and the pressure decrease is maintained for at least 24 hours.
Elimination: The metabolites are mainly eliminated by renal way. Approximately 88% and 98% of the administered dose can be recovered in urine, after the ophthalmic topical and intravenous administration, respectively.

Posology and Way of administration:
In adults and the elder, the recommended dose is 1 drop of LOUTEN® ophthalmic emulsion into the affected eye(s) 1 time a day. The optimum effect is obtained when the product is administered during the first hours in the evening.
The single daily administration should be carefully observed, since it is proved that the increase of the daily dose decreases the reducing effect of the intraocular pressure.
If the administration of one dose is missed, treatment should be resumed at the habitual next dose without doubling it up.
As with any other eye drops, it is recommended to press the lacrimal sac with the finger for one minute right after instilling each drop, in order to reduce possible systemic absorption.
The instillation of other ophthalmic topical medication should be conducted after at least 5 minutes after the administration of LOUTEN® ophthalmic emulsion.
Patients using contact lenses should remove the lenses before administering LOUTEN® ophthalmic emulsion and wait for 15 minutes before instilling again.

Contraindications:
Known hypersensitivity to any product components.

Warnings:
Before administering LOUTEN® ophthalmic emulsion treatment, patients should be informed about the possibility of experiencing a change of the iris color, since Latanoprost can gradually increase the iris brown pigment. This effect was more frequently seen in patients with mixed colored iris such as: blue-brown, gray-brown, green-brown, or yellow-brown due to an increase of the melanin content in the iris stroma melanocytes. Patients with homogeneously colored eyes, such as blue, gray, green, or brown, the color changing was rarely seen in treatments of up to 2 years. Tipically, the brown pigmentation around the pupil concentrically spreads towards the periphery; when the eye is affected, this iris may become more brownish in some areas or completely brown. Neither the iris nevus nor the iris freckles are affected by the treatment. No pigment accummulation was seen in either the trabecular mesh or in any other area of the anterior chamber. The iris color change may not be noticed until several months or years have elapsed, and it is unrelated to any symptom or pathological change. After treatment discontinuation, the eye pigmentation does not increase, but the color change may remain and be permanent. Unilateral treatment may result in permanent heterochromia (eye color change in relation to the other eye). Until data from several follow-up years of clinical studies are available, patients with mixed colored iris are recommended to be treated with LOUTEN® ophthalmic emulsion only when exhibiting lack of tolerability or when the response to other ocular hypotensive agents is not enough.

Precautions:
Product is packed in sterile conditions. The dropper tip should be correctly handled avoiding contact with the eye, eyelashes, and adjacent areas, or with any other surface in order to avoid bacterial contamination commonly resulting in ocular infections.
Using contaminated products may cause serious eye damage and vision loss.
Until more information about the increase of the iris brown pigmentation is available, patients should be regularly tested and, depending on the clinical background, determine if it would be necessary to suspend treatment in case of increase of the iris pigmentation.
No experience about the use of LOUTEN® ophthalmic emulsion in the treatment of inflammatory and neo-vascular glaucoma, inflammatory ocular conditions, or congenital glaucoma is available, and limited experience is available on the treatment of closed angle chronic glaucoma, open angle glaucoma in patients with pseudophakia, and pigmentary glaucoma. Therefore, precaution is recommended when using the product for treating these conditions.
Drug-drug interactions:
No final drug-drug interaction data are available. There are reports about paradoxical intraocular pressure increases after the concomitant ophthalmic topical administration of two prostaglandin analogue agents. In vitro studies prove that when solutions containing Thimerosal and Latanoprost are mixed up, precipitation occurs; in this case, medications should be administered after at least 5 minutes in between instillations.
Carcinogenesis - Mutagenesis - Fertility impairment
Latanoprost proved not to be mutagenic in tests conducted on bacteria, in murine lymphoma models, or in murine micronucleous tests. Chromosomal alterations in human lymphocytes were seen in in vitrostudies. Latanoprost did not prove to be cause carcinogenic action in studies conducted in mice and rats. Latanoprost has not proved to cause any effect on male or female animal fertility.
Pregnancy
No suitable and well controlled studies in pregnant women are available. LOUTEN® ophthalmic emulsion should be used during pregnancy only when the potential benefits for the mother justifies the potential risk for the fetus.
Lactation
Latanoprost and its metabolites are excreted into breast milk; therefore, precaution is required when administering LOUTEN® ophthalmic emulsion to nursing women. Also, lactation interruption could be considered.
Pediatric use
Product efficacy and tolerability have not been determined in children.
Renal and hepatic impairment
Latanoprost has not been studied in these patients; therefore, precaution is required when used with them.
Effects on the capability of driving or using machinery
As with other ophthalmic products, instilling eyedrops may cause transient blurred vision; therefore, patients should not drive vehicles or operate machinery until this effect no longer happens.

Adverse reactions:
Ocular:
Very frequent (5% al 15%): Blurred vision, burning and pricking sensation, conjunctival hyperemia, foreign body sensation, itching, increase of iris pigmentation and punctuate epithelial keratopathy.
Frequent (1% to 4%): Dry eye, tearing, eye pain, palpebral crust, palpebral edema, palpebral erythema, palpebral pain/discomfort, and photophobia.
Less frequent (<1%): Conjunctivitis, diplopia, and conjunctival secretion.
Rare: Retinal artery embolism, retinal detachment, and vitreous body hemorrhage of diabetic retinopathy.
Systemic:
The most frequently observed systemic adverse events with the use of Latanoprost were the following:
Respiratory: Infection of the respiratory tract, cold, flu (4%).
Cardiac: Chest pain, chest angina (1-2%).
Cutaneous: Rash, allergic cutaneous reaction (1-2%).
Muscular: Muscle pain, joint pain, back pain (1-2%).

Overdose:
Besides the ocular irritation and conjunctival or episcleral hyperemia, no other ocular adverse effects of Latanoprost are known when it is administered at high doses. The intravenous administration of high doses to monkeys has been related to transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with Latanoprost, no bronchoconstriction was observed. In case of overdose of Latanoprost, symptomatic treatment should be administered.
In case of accidental ingestion or overdose, go to the nearest hospital or call the following toxicology centers.

How supplied:
Package containing 2.5 ml of sterile ophthalmic emulsion.

INFORMATION FOR PATIENTS

"Carefully read this information before using this medication. Keep this package insert since you may need to read it again. If you have any doubts, tell your physician or pharmacist. This medication has been prescribed only to you, do not either administer or recommend it to other people, even though they may suffer from the same symptoms as you, since it could be harmful. This information is not intended to replace talking to your physician about your disease or treatment. This treatment should be indicated and prescribed by your physician. If you consider that some of these adverse effects are severe or if any undesirable event occurs, which is not listed in this package insert, inform your physician or pharmacist".

WHAT IS LOUTEN® AND WHAT IS IT USED FOR?
LOUTEN® is a medication used for treating diseases such as open angle glaucoma and ocular hypertension related to pressure increase inside the eye.
LOUTEN® increases the outflow of liquid from inside the eye into the blood stream and, consequently, reduces the intraocular pressure.

WHAT DO I NEED TO KNOW BEFORE USING LOUTEN®?
LOUTEN® can be used by men and women (including older people).
Pregnancy: Pregnant patients should tell their doctor before using the product; LOUTEN® can be used during pregnancy based on medical decision and control and when the potential benefit justifies the potential risk for fetus.
Lactation: Nursing patients should tell their doctors before using LOUTEN® due to possible serious adverse reactions to infants, lactation discontinuation or treatment interruption should be considered based on how important this product is for the mother.
Gradual eye color change: The iris color may change as a result of an increase in the amount of Brown pigment. If the color of your eyes is mixed (blue-brown, gray-brown, green-brown or, yellow-brown), the probability of suffering from this change is greater than if your eyes have a single color (blue, gray, green, or brown). The eye color change takes years to happen, even though it can be noticed after a few months of treatment. The iris color change can be permanent and can be more noticeable if the product is used in only one eye. This color change seems not to be related to the manifestation of any problem. Once that treatment was suspended, the color change does not progress.
Driving vehicles and using machinery: When instilling the product, blurred vision may be present for a short period of time; if this happens, do not drive any vehicles or use tools or machinery until your vision is sharp again.

WHO SHOULD NOT USE LOUTEN®?
Allergic patients (hypersensitive) to Latanoprost or to any components of the formula.

HOW SHOULD LOUTEN® BE USED?
Follow medical directions.
In adults (including the elder), the recommended dose is 1 drop in the affected eye(s) 1 time a day, preferably in the evening. Do not use the product more than 1 time a day, since treatment efficacy may decrease. If you miss one dose, resume the following habitual dose without doubling it. Use LOUTEN® as it was indicated by your physician and until your physician tells you to do so. If you use other eye drops, wait at least 5 minutes in between instillations.
In order to instill the drops, do the following:
1. Wash your hands.
2. Remove the dropper cap.
3. Softly move the lower eyelid of the affected eye downwards with your finger.
4. Place the dropper tip closet o eye without touching it.
5. Press the dropper so as only one drop falls into the eye and then remove the finger.
6. Press the corner of the affected eye with your finger in the area close to the nose. Keep the finger pressure for 1 minute while the eye is close.
7. Repeat the operation in the other eye if your physician tells so.
8. Close the dropper correctly.

Patients who use contact lenses should remove the lenses before administering LOUTEN® and wait for 15 minutes before placing the lenses back.

POSSIBLE ADVERSE EFFECTS
As with other medications, LOUTEN® may cause adverse effects. The following are known adverse effects:
Ocular:
Very frequent (5% to 15% of treated patients):
Gradual eye color change, blurred vision, ocular reddening, ocular irritation (burning and pricking sensation, foreign body sensation, itching).
Frequent (1% to 4% of treated patients):
Dry eye, tearing, eye pain, eyelid inflammation, and light sensibility.
Less frequent (<1% of treated patients):
Conjunctivitis, double vision, and conjunctival secretion.
Rare:
Retinal artery embolism and hemorrhage.
Systemic:
The most common systemic adverse events observed with Latanoprost are:
Respiratory: Infection of the respiratory tract, common cold, flu (4%).
Cardiac: Chest pain, chest angina (1-2%).
Cutaneous: Rash, allergic cutaneous reaction (1-2%).
Muscular: Muscle pain, joint pain, back pain (1-2%).
Children:
Efficacy and tolerability in children have not been determined.

ADDITIONAL INFORMATION
The active ingredient of LOUTEN® is Latanoprost 0.005% (50 micrograms per milliliter).
The other components are: Médium-Chain triglycerides, Polysorbate 80, Polyethylene glycol 400, Boric acid, Potassium sorbate, Glycerin, Disodium edetate dihydrate, 1N Sodium hydroxide dissolved in Purified water.

PREVENTION OF CONTAMINATION
The product is packed in sterile conditions. The dropper tip should be correctly handled avoiding contact with the eye, eyelashes, and eye adjacent areas, or any other surface in order to avoid commonly bacterial contamination resulting in eye infections. Using contaminated products may cause serious eye damage and consequently, vision loss.

Storage conditions:
Store at room temperature from 15°C to 30°C. Protect from light.
After opening the container for the first time, use the content within 4(four) weeks.
Do not use the product after the expiration date.

Keep medicaments out of the reach of children.

To be administered under prescription and medical surveillance.

Manufactured by:
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