LOUTEN T®

LATANOPROST 0.005%
TIMOLOL 0.5%

STERILE OPHTHALMIC SOLUTION
Made in Argentina - Rx ONLY

Formula:
Each ml of solution contains:
Latanoprost 50 µg
Timolol (as Maleate) 5mg
Benzalkonium chloride 0.2 mg; Sodium chloride 3.2 mg; Monosodium phosphate monohydrate 4.6 mg; Disodium phosphate anhydrous 4.74 mg; Purified water, q.s.

Therapeutical action:
Combination for topical ophthalmic use of a prostaglandin $F_{2\alpha}$ analogue (latanoprost) and a beta-adrenergic receptor blocking agent (Timolol).
ATC Classification: SO1ED. Antiglaucomatous.

Indications:
Treatment of high intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma, when a local treatment with a combination of a prostaglandin $F_{2\alpha}$ analogue and a beta-adrenergic receptor blocking agent is indicated; and in patients with intolerance or insufficient response to other treatments.

Pharmacological characteristics/Properties:
LOUTEN T® contains two active ingredients in its formula: Latanoprost and Timolol. Both components of the formula reduce the increased intraocular pressure. Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective antagonist of the FP prostanoid receptor that reduces the intraocular pressure, increasing the outflow of the aqueous humour, and which main mechanism of action is the increased uveoscleral outflow.
Elimination
Metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose may be recovered in the urine, following topical ophthalmic and intravenous administration, respectively.
Timolol pharmacokinetics
The beginning of the Timolol action is observed within the first hour following application, manifesting its maximum effect between 1 and 2 hours later. A significant reduction may be kept during periods of up to 24 hours with a unique dose. At the beginning the treatment a reduction of the intraocular pressure of 40% or more can arise, but in the long term, the drug effect may be reduced and just may be expected a decrease in the intraocular pressure of 20-25%. Timolol produces an hypotensor effect in the non-treated eye, which may be originated by a secondary local effect or a systemic action.
LOUTEN T® Pharmacokinetics
No pharmacokinetic interaction is observed between Timolol and Latanoprost; although an increase of about twofold of Latanoprost acid concentration has been observed in the aqueous humour, after 1 to 4 hours from LOUTEN T® instillation, compared to the concentration recorded with the monotherapy.

Dosage and Administration:
In adults and elderly subjects, the recommended dosage is 1 drop of LOUTEN T® in the affected eye(s), q.d. during the morning.
The single daily dose should not be exceeded since it has been shown that the increased daily dose decreases the intraocular pressure lowering effect.
The instillation of other ophthalmic drops requires at least a five minute-interval after LOUTEN T® administration. Patients wearing contact lenses should remove them before applying LOUTEN T® and then wait 15 minutes to reinsert them.
If a dose is missed during the treatment, the following usual dose should be applied, without being duplicated.

Contraindications:
Known hypersensitivity to any components of the formula. Bronchial asthma or a history of bronchial asthma or severe chronic obstructive pulmonary disease.
Sinus bradycardia; Second or third degree atrioventricular block; overt heart failure; cardiogenic shock.
Timolol is a non-selective beta adrenergic receptor blocking agent, which does not have intrinsic sympathomimetic activity, significant direct myocardial depressant or local anaesthetic activity (membrane stabilizer) and lowers increased intraocular pressure by reducing aqueous humour production. The combined effect of these two active ingredients produces a further decrease of the intraocular pressure when compared to the one obtained with any of these components administered alone. Ocular topical administration of LOUTEN T® reduces the increased intraocular pressure, either glaucoma is present or not.
LOUTEN T® reduces the increased intraocular pressure without the common side effects of antiglaucomatous parasympathomimetic agents, such as accommodative spasm or miosis. Lowering of the intraocular pressure starts about 1 hour following the administration of LOUTEN T® and the maximum effect is reached within 6 to 8 hours. The intraocular pressure lowering effect is adequately maintained at least during 24 hours following instillation.
Latanoprost pharmacokinetics
Absorption: Latanoprost is an isopropyl ester prodrug. Latanoprost is absorbed through the cornea and there is hydrolyzed by esterases to Latanoprost acid which is the biologically active compound.
Distribution: The distribution volume of Latanoprost is 0.16 ± 0.02 L/kg.
Latanoprost has been measured in aqueous humour during the first four hours and in plasma during the first hour after topical ophthalmic administration.
Biotransformation: Latanoprost is an isopropyl ester prodrug. Latanoprost is hydrolyzed by esterases in the cornea to Latanoprost acid, which is the biologically active compound.
Latanoprost portion reaching the systemic circulation is biotransformed by the liver to 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid beta-oxidation.
Half-life: The elimination of latanoprost acid from plasma is rapid (half-life = 17 minutes) after both ophthalmic and intravenous administration.
Latency time: About 3 or 4 hours following administration.
Maximum concentration time: The maximum concentration in the aqueous humour, approximately 15 - 30 ng/ml, is reached about 2 hours following ophthalmic administration of latanoprost.
Maximum effect time: Eight to twelve hours after topical ophthalmic administration.

Warnings and Precautions:
Cardiorrespiratory effects - As with other topically applied ophthalmic products, this medication may be absorbed systemically. The Timolol component is a beta-adrenergic blocking agent, and therefore, the same adverse reactions observed with the systemic administration of beta-adrenergic blocking agents may occur. Because of the presence of Timolol, heart failure should be appropriately compensated before starting the treatment with LOUTEN T®. In patients with a history of severe cardiopathy, possible signs of heart failure should be monitored and the heart rate frequency should be controlled. Heart and respiratory reactions, including death caused by a brochospasm in patients with asthma, and rarely, death related to heart failure, have been reported following the administration of Timolol ophthalmic solution.
LOUTEN T® has not been studied in patients with renal or hepatic impairment; therefore the product should be used with caution in such cases.
Concomitant treatments - Patients who are being treated with a systemic beta-adrenergic blocking agent and receive LOUTEN T® should be monitored due to the probability of additive effects on both the intraocular pressure and the known systemic effects of the beta-adrenergic blocking agents. The concomitant use of two topical beta-adrenergic blocking agents or two local prostaglandins is not recommended.
Closed-angle glaucoma - The treatment of patients with closed-angle glaucoma requires other therapeutical interventions, in addition to topical hypotensive agents. LOUTEN T® has not been studied in patients with acute closed-angle glaucoma.
Choroid detachment has been informed with the administration of suppressor agents of the aqueous humour production (for example, Timolol and Acetazolamide).
Latanoprost is hydrolyzed in the cornea. Patients may slowly develop an increasing brown pigments in the iris. This change may not be observed during months or years. Typically the brown pigmentation around the pupil is concentrically spread towards the affected eyes periphery, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be regularly examined and, depending on the clinical situation, treatment may be stopped if increased pigmentation occurs. During clinical researches, the increased brown iris pigment has not been shown to progress further upon treatment discontinuation, but the resultant colour change may be permanent. Neither nevi nor freckles of the iris have been affected by treatment.
There is no experience with the use of LOUTEN T® in inflammatory, neovascular, narrow angle or congenital glaucoma; and there is limited experience as regards open-angle glaucoma in patients with pseudophakia and pigmentary glaucoma.

Patient information:
Patients should be informed about the possibility of iris colour change due to an increased brown pigment and its possible resultant cosmetic different that may occur when only one eye is treated. Iris pigmentation changes may be more noticeable in patients with green-brown, blue/grey-brown or yellow-brown iris.
Patients should be instructed to avoid the dropper tip to be in contact with the eye or surrounding structures since it may cause tip contamination by bacteria commonly known to cause ocular infections. The use of contaminated solutions may result in serious eye damage and the subsequent loss of vision.
If patients develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should also be instructed to immediately seek their physician's advice concerning the continued use of the multidose container that they have been using.
Patients should be advised that if they develop any ocular reactions, specially conjunctivitis and palpebral reactions, they should immediately seek for their physician's advice. Patients should also be informed that LOUTEN T® ophthalmic solution contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed before the solution administration. Said lenses may be reinserted 15 minutes following LOUTEN T® administration.
If more than one topical ophthalmic drug is being used, the drugs should be administered at least with a 5 (five) minute-interval.
Interactions
In vitro studies show that precipitation occurs when solutions containing thimerosal are mixed with LOUTEN T®. If this is the case, drugs should be administered with an interval of at least 5 (five) minutes between applications. There may be additive effects and marked hypotension and/ or bradycardia when administering timolol ophthalmic solution together with calcium channel blockers, substances causing beta-adrenergic blocking agents or catecholamine depletion.
Potentiated systemic beta-blockade has been reported during combined treatment with timolol and quinidine, possibly because quinidine inhibits the timolol metabolism by the P-450 CYP2D6 enzyme.
Beta blocking agents may increase the hypoglycaemic effect of antidiabetic agents.
Pregnancy
No specific studies with LOUTEN T® have been carried out in pregnant women. Preclinical studies carried out with Latanoprost show a toxicity in reproduction. Potential risk in human being is not known.
Timolol: controlled epidemiological studies, carried out with systemically used beta-blocking agents do not produce malformations; although, some pharmacological effects, such as bradycardia in the fetus and neonates, have been observed.
Consequently, LOUTEN T® should not be administered during pregnancy.
Lactation
It has not been established whether Latanoprost or its metabolites are excreted in human milk. Timolol maleate is certainly detected in maternal milk. Due to the possibility of serious adverse reactions in the infant, a decision between interrupting either treatment or breastfeeding should be taken according to the relevance the product has for the mother.
Pediatric use
Safety and effectiveness of LOUTEN T® in pediatric patients have not been established.

Adverse reactions:
LOUTEN T® is generally well tolerated. No specific adverse reactions have been recorded for LOUTEN T®, consequently, the adverse events are limited to those reported for Latanoprost and Timolol individually.
Based on the evidence of photographic sequences, the increased iris pigmentation has been recorded in 16-20% of all patients treated with a fixed combination of Latanoprost/Timolol during a period of at least 1 year.
LOUTEN T® may result in gradual changes in eyelashes of the treated eye, these changes include: increased length, thickness, pigmentation and/or number of eyelashes, which were observed in 37% of the patients.
Other adverse reactions more frequently reported in clinical test were: ocular irritation, including stinging, burning and itching (12%), conjunctival hyperemia (7.4%), corneal disorders (3%), conjunctivitis (3%), blepharitis (2.5%), ocular pain (2.3%), headache (2.3%) and rash/allergic cutaneous reaction (1.3%).
Additional adverse reactions that have been observed with some of the components and may potentially occur with LOUTEN T® are:
Ocular: punctate epithelial keratopathy, periorbital edema, corneal edema and erosions, macular edema (in pseudophakic and aphakic patients or in those patients with known risk factors of macular edema), iritis/uveitis. Signs and symptoms of ocular irritation, including blepharitis, keratitis, corneal decreased sensitivity and ocular dryness; visual disturbances including refractive changes, diplopia, ptosis, tinnitus.
Respiratory: asthma, asthma exacerbation and dyspnea. Bronchospasm (mainly in patients with pre-existing bronchospastic diseases), cough.
Dermal: darkening of parpebral skin.
Cardiovascular: bradycardia, arrhythmia, hypotension, syncope, heart block, stroke, cerebral ischemia, congestive heart failure, palpitations, heart attack, edema, claudication, Reynaud`s phenomenon, cold hands and feet.
Hypersensitivity: signs and symptoms of allergic reactions, including angioedema, urticaria, localized and generalized allergic reaction/ rash.
Nervous system/psychiatry: fainting, depression, insomnia, nightmares, loss of memory, increased signs and symptoms of miastenia gravis, paresthesia.
Digestive: nausea, diarrhea, dyspepsia, mouth dryness.

Overdosage:
There is no available data on accidental or intentional overdosage with LOUTEN T® in human beings. Accidental overdosage with Timolol ophthalmic solution results in systemic effects, similar to those observed with systemic beta-adrenergic receptor blocking agents, such as dizziness, headache, respiratory distress, bradycardia, bronchospasm and heart arrest. Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of Latanoprost administered at high doses are not known.
Intravenous administration of high doses of Latanoprost in monkeys has been associated with transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with Latanoprost, bronchoconstriction was not observed.
The treatment should be symptomatic and supportive. Electrolyte serum levels (mainly potassium) and pH blood values should be monitored. Studies have shown that Timolol is not easily dialyzable.
In case of accidental overdosage or administration, go to the nearest hospital or toxicology centers.

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

Storage conditions:
Keep in refrigerator between 2 and 8°C. Protect from light.

Discard the product after 1 month of being opened and store at room temperature below 25°C.

Keep drugs out of reach of children

Delicate use product. To be administered under prescription and medical surveillance.

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