GLAUCOTENSIL® TD

DORZOLAMIDE 2%
TIMOLOL 0.5%

Poen

STERILE OPHTHALMIC SOLUTION

Made in Argentina - Rx ONLY

Formula:
Each 100 ml of solution contains:
Dorzolamide HCl (base equivalent to 2000 mg) 2226.0 mg
Timolol maleate (base equivalent to 500 mg) 683.0 mg
Sodium citrate; Hydroxyethylcellulose; Sodium hydroxide solution q.s. pH 5.5; Mannitol; Benzalkonium chloride 7.5 mg; Purified water, q.s.

Therapeutical action:
Combination for topical ophthalmic use of a carbonic anhydrase inhibitor (Dorzolamide) and a beta-adrenergic receptor blocking agent (Timolol).
ATC Classification: S01E. Antiglaucomatous.

Indications:
It is indicated for the treatment of increased intraocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other open-angle secondary glaucomas when a local treatment with a combination of a carbonic anhydrase inhibitor and a beta-adrenergic receptor blocking agent is indicated.

Pharmacological characteristics:
GLAUCOTENSIL® TD has in its formula two active ingredients: Dorzolamide hydrochloride and Timolol maleate. Both components of the formula reduce increased intraocular pressure by reducing aqueous humour production through different mechanisms of action. Dorzolamide is a potent inhibitor of the human carbonic anhydrase II. Inhibition of the carbonic anhydrase in eye ciliary processes reduces the aqueous humour production, inhibiting bicarbonate ion synthesis with the consequent reduction in the sodium and fluids transportation.
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). 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 GLAUCOTENSIL® TD reduces the increased intraocular pressure, either glaucoma is present or not.
GLAUCOTENSIL® TD reduces the increased intraocular pressure without the common side effects of antiglaucomatous parasympathomimetic agents, such as accommodative spasm or miosis.

Dosage and administration:
The recommended dosage is one drop of GLAUCOTENSIL® TD in the affected eye(s) twice a day, every 12 hours. When other antiglaucomatous agent(s) of ophthalmic topical use are replaced by GLAUCOTENSIL® TD, they should be discontinued after being properly administered during this day and started with GLAUCOTENSIL® TD the following day. If other topical ophthalmic products are being used, GLAUCOTENSIL® TD and the other products should be administered at least with a 10-minute interval.

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. Severe renal impairment (CrCl< 30mL/min) or hyperchloraemic acidosis.

Warnings:
For ophthalmic topical use only.
DO NOT INJECT. GLAUCOTENSIL® TD is intended exclusively for ophthalmic topical use.
Do not use the medicine after the indicated expiration date.
Use the product only if the package is intact.
If the condition worsens and persists more than 72 hours, pain or alterations of the vision appear and/or the eye irritation is worsen, suspend the use of the product and consult with a professional.
GLAUCOTENSIL® TD formulation contains Benzalkonium Chloride as preservative, which may be deposited or absorbed by soft contact lenses. Therefore, GLAUCOTENSIL® TD should not be applied while wearing contact lenses. The lenses should be removed prior to the administration of GLAUCOTENSIL® TD drops and they should not be reinserted for a 15-minute period after the administration.
There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the corneal epithelial surface.

Precautions:
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. For example heart and respiratory reactions, including death caused by a bronchospasm in patients with asthma, and rarely, death related to heart failure, have been reported following the administration of Timolol maleate ophthalmic solution.
Cardiac disorders - Because of the presence of Timolol maleate, heart failure should be appropriately compensated before starting the treatment with GLAUCOTENSIL® TD. In patients with a history of severe cardiopathy (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with betablockers, possible signs of heart failure should be monitored and the heart rate frequency should be controlled.
Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta adrenergic receptor blockade may precipitate more severe failures.
In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, GLAUCOTENSIL® TD should be discontinued.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.
Vascular disorders - Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's syndrome) should be treated with caution.
Respiratory disorders - Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which GLAUCOTENSIL® TD is contraindicated) should, in general, not receive beta-blocking agents including GLAUCOTENSIL® TD.
Potentiation of Muscle weakness - Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
Renal and hepatic failure - GLAUCOTENSIL® TD has not been studied in patients with severe renal failure (creatinina clearance < 30 ml/min). As dorzolamide and its metabolite are excreted mainly through the kidneys, the use of GLAUCOTENSIL® TD is not recommended in these patients.
GLAUCOTENSIL® TD has not been studied in patients with hepatic impairment; therefore the product should be used with caution in such cases.
Hypersensitivity - As with other topical ophthalmic agents, the product active ingredients may be absorbed systemically. Dorzolamide is a sulphonamide and therefore, the same adverse reactions observed with sulfonamides sistemic administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, may occur. If any signs of serious reaction or hypersensitivity are developed, discontinue the product application.
In clinical studies, ocular adverse effects have been reported, mainly conjunctivitis and palpebral reactions, with the long-term administration of Dorzolamide hydrochloride in ophthalmic solution. Some of these reactions had the appearance and course of an allergic-type reaction and they were resolved upon treatment discontinuation. Similar reactions have been observed with the combination of Dorzolamide hydrochloride-Timolol maleate. In case said reactions are observed, the treatment with GLAUCOTENSIL® TD should be discontinued. While they were treated with beta-adrenergic blocking agents, patients with a history of atophy or severe anaphylactic reaction to allergens may be more susceptible to repeated therapeutical, diagnostic or accidental exposure to such allergens. Those patients may not respond to usual doses of epinephrine, used for the treatment of anaphylactic reaction.
Diabetes Mellitus - Beta-adrenergic blocking agents should be administrated with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.
Thyrotoxicosis - Beta-adrenergic blocking agents may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.
Major Surgery - The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic receptor blocking agents may be reversed by sufficient doses of adrenergic agonist.
Withdrawal of therapy - As with systemic beta-blockers, if discontinuation of ophthalmic Timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.
Corneal diseases - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing GLAUCOTENSIL® TD to this group of patients.
Acid-base disturbances - Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with this medicinal product, urolithiasis has been reported infrequently. Because GLAUCOTENSIL® TD contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients with a prior history of renal calculi may be at increased risk of urolithiasis while using this medicinal product.
Concomitant treatments - There is a possibility of a sum effect as regards the known systemic effects due to the carbonic anhydrase inhibition in patients concomitantly treated with oral and topical carbonic anhydrase inhibitors.
The concomitant administration of GLAUCOTENSIL® TD and oral carbonic anhydrase inhibitors is not recommended.
Patients who are being treated with a systemic beta-adrenergic blocking agent and receive GLAUCOTENSIL® TD 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 is not recommended.
Closed-angle glaucoma - The treatment of patients with closed-angle glaucoma requires other therapeutical interventions, in addition to topical hypotensive agents. GLAUCOTENSIL® TD 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).

Interactions
No specific interaction studies have been carried out with GLAUCOTENSIL® TD.
During the clinical studies course, the combination of Dorzolamide hydrochloride-Timolol maleate was used concomitantly with the following systemic products, with no evidence of adverse interactions: ACE inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs (including acetylsalicylic acid) and hormones (oestrogen, insulin, thyroxine). However, there may be additive effects and marked hypotension and/or bradycardia when administering Timolol maleate 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.
Dorzolamide is a carbonic anhydrase inhibitor and, although it is topically administrated, as it was mentioned before, it is absorbed systemically. Dorzolamide hydrochloride ophthalmic solution was not associated to acid-base balance disorders. However, such disorders have been reported with oral carbonic anhydrase inhibitors and, in some instances, they have resulted in drug interactions (e.g. toxicity associated with high-dose salicylate therapy). Therefore, this possibility and said interactions should be considered in patients treated with GLAUCOTENSIL® TD. Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.
Although GLAUCOTENSIL® TD alone has little or no effect on pupil size, mydriasis resulting from the concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
Beta-blockers may increase the hypoglycemic effect of antidiabetic agents.

Pregnancy
No specific studies with GLAUCOTENSIL® TD have been carried out in pregnant women. GLAUCOTENSIL® TD may be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus.

Lactation
It is not known whether Dorzolamide is excreted in maternal milk.
Timolol Maleate has been detected in maternal milk. Because of the possibility for serious adverse reactions in infants, 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 GLAUCOTENSIL® TD have not been established in children.

Adverse reactions
GLAUCOTENSIL® TD is generally well tolerated. The most frequent adverse reactions were taste disturbances (bitter, acid or unusual taste) and burning, or stinging sensation in the eyes in up to 30% of patients. In 5 to 15% of the cases, conjunctival hyperemia, blurred vision, superficial keratitis and ocular itching have been reported. The following adverse effects were reported in 1 to 5% of patients: abdominal pain, back pain, blepharitis, bronchitis, blurred vision, conjunctival discharge, conjunctival edema, conjunctival follicles, conjunctival injection, conjunctivitis, corneal erosion, corneal spots, opacity of the lens, cough, vertigo, eye dryness, dyspepsia, ocular detritus, ocular secretion, ocular pain, lacrimation, palpebral edema, palpebral sweating, pain or discomfort, foreign body sensation, glaucomatous excavation, headache, hypertension, flu, lens nucleus coloration, opacity of the lens, nauseas, opacity of the lens nucleus, faryngitis, posterior subcapsular cataract, sinusitis, upper airway infection, urinary tract infection, visual field fault, vitreous detachment.
The following adverse events occurred either with a low incidence (<1%) in the course of he clinical studies or have been reported voluntarily during the use in the clinical practice, although neither the population size nor the frequency may be established accurately. They have been selected, based on factors such as seriousness, communication frequency, possible causal connection with the association of Dorzolamide hydrochloride + Timolol Maleate, or a combination of them all: bradycardia, heart failure, chest pain, strokes, depression, diarrhea, mouth dryness, dyspnea, hypotension, iridociclitis, myocardial infarction, nasal congestion, skin eruption, paresthesia, photophobia, urolithiasis and vomiting. Other adverse reactions that have been reported for Dorzolamide or Timolol were: hypersensitivity reactions (signs and symptoms of local reaction including eyelid reaction and systemic allergic reactions such as, angioedema, bronchospasm, pruritus, urticaria), reactions on skin and subcutaneous tissue disorders (contact dermatitis, epistaxis, throat irritation), of special sense (eyelid crusting, ocular allergic reaction, transient myopia). Although another adverse reactions such as fatigue, asthenia, arrhythmia, syncope, cerebral ischemia, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, cold feet and hands, anorexia, systemic lupus erythematosus, increase in signs and symptoms of myasthenia gravis, somnolence, insomnia, nightmares, behavioral changes, psychic disturbances (confusion, hallucinations, anxiety, disorientation, nervousness and memory loss), alopecia, psoriasiform rash or exacerbation of psoriasis, masked symptoms of hypoglycemia in diabetic patients, ptosis, decreased corneal sensitivity, cystoid macular edema, visual disturbances, pseudopemphigoid, tinnitus, retroperitoneal fibrosis, decreased libido, impotence, Peyronie's disease, dizziness, corneal edema, ocular hypotony, choroidal detachment (following filtration surgery), diplopia, cardiac failure, cardiac arrest, heart block, atrioventricular block, shortness of breath, respiratory failure, rhinitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and myalgia have been reported.

Overdosage:
There is no available data on accidental or intentional overdosage with GLAUCOTENSIL® TD in human beings. Accidental overdosage with Timolol maleate 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. The most common signs and symptoms that may be expected with Dorzolamide overdosage would be, electrolyte imbalances, acidosis and central nervous system effects. The treatment would 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:
GLAUCOTENSIL® TD: Package with 1 dropper bottle, containing 5 ml of ophthalmic solution.

Storage conditions:
Store below 30°C. Protect from light.

Once the container is opened for the first time, it should be used within 4 weeks.

Keep drugs out of reach of children.

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

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