115 (L) x 165 (H) mm ***FRONT***

MedChoice™ Vision Care

℞

Dorzolamide + Timolol

Dorzodin® Plus

20 mg / 5 mg per mL (2.0 % / 0.5 % w/v)
Sterile Ophthalmic Solution (Eye drops)
ANTI-GLAUCOMA

PRODUCT DESCRIPTION:
A colorless or pale yellow colour liquid.

FORMULATION/COMPOSITION:
Each mL contains:
Dorzolamide hydrochloride BP
Eq. to Dorzolamide ..... 2.0% w/v
Timolol maleate USP
Eq. to Timolol ..... 0.5% w/v
Benzalkonium chloride solution BP ..... 0.02% v/v

PHARMACODYNAMIC AND PHARMACOKINETICS:
Dorzolamide + timolol eye drops is comprised of two components: Dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intra-ocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action. Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intra-ocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intra-ocular pressure reduction compared to either component administered alone.

PHARMACODYNAMICS:
Clinical effects:
Clinical studies of up to 15 months duration were conducted to compare the IOP-lowering effect of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution BID (dosed morning and bedtime) to individually and concomitantly administered 0.5% timolol and 2.0% dorzolamide in patients with glaucoma or ocular hypertension for whom concomitant therapy was considered appropriate in the trials. This included both untreated patients and patients inadequately controlled with timolol monotherapy. The majority of patients were treated with topical beta-blocker monotherapy prior to study enrollment. In an analysis of the combined studies, the IOP-lowering effect of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution BID was greater than that of monotherapy with either 2% dorzolamide TID or 0.5% timolol BID. The IOP-lowering effect of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution BID was equivalent to that of concomitant therapy with dorzolamide BID and timolol BID. The IOP-lowering effect of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution BID was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.
Pediatric use:
A 3-month controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under 6 years of age and greater than or equal to 2 years, whose IOP was not adequately controlled with dorzolamide or timolol monotherapy, received dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution in an open-label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

PHARMACOKINETICS:
Dorzolamide hydrochloride:
Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the active substance to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors. When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, active substance and metabolite concentrations in red blood cells (RBCs) and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as result of selective bending to CA-II while extremely low concentrations of free active substance in plasma are maintained. The parent active substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent active substance but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%), dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washed out of RBCs non-linearly, resulting in a rapid decline of active substance concentration initially, followed by a slower elimination phase with a half-life of about four months.
When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free active substance or metabolite in plasma; CA inhibition in RBCs was less than anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 mL/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.
Timolol maleate:
In a study of plasma active substance concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

INDICATIONS:
Dorzolamide + timolol eye drops is indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION:
The dose is one drop of Dorzolamide + timolol eye drops in the conjunctival sac of the affected eye(s) two times daily.
If another topical ophthalmic agent is being used, Dorzolamide + timolol eye drops and the other agent should be administered at least ten (10) minutes apart.
If one dose is missed, treatment should continue with the next dose as normal. The duration of the treatment should be as recommended by the doctor.
Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.
Pediatric use:
Efficacy in pediatric patients has not been established.

CONTRAINDICATIONS:
Dorzolamide + timolol eye drops solution is contraindicated in patients with:

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- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock
- Severe renal impairment (CrCl 30 mL/min) or hyperchloremic acidosis
- Hypersensitivity to one or both active substances or to any of the excipients listed

The above are based on the components and are not unique to the combination.

PREGNANCY AND LACTATION:
Pregnancy:
Dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution should not be used during pregnancy.
Lactation:
If treatment with dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution is required, then lactation is not recommended.

INTERACTIONS:
No specific drug interaction studies have been performed with dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution. In clinical studies, dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g., estrogen, insulin, thyroxine). There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, catecholamine-depleting medicines or beta adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine, narcotics and monoamine oxidase (MAO) inhibitors.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine) and timolol. Although dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. Beta-blockers may increase the hypoglycemic effect of antidiabetic agents. Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

ADVERSE DRUG REACTIONS:
Clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Dorzolamide-timolol fixed dose combination was evaluated for safety in 1,035 patients with elevated intraocular pressure treated for open-glaucoma or ocular hypertension for up to 15 months. Approximately 5% of all patients discontinued therapy because of adverse reactions. The most frequently reported adverse reactions occurring in up to 30% of patients were taste perversion (bitter, sour or unusual taste) or ocular burning and/or stinging. The following adverse reactions were reported in 5 to 15% of patients: conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching. The following adverse reactions were reported in 1-5% of patients: abdominal pain, back pain, blepharitis, bronchitis, cloudy vision, conjunctival discharge, conjunctival edema, conjunctival follicles, conjunctival injection, conjunctivitis, corneal erosion, corneal staining, cortical lens opacity, cough, dizziness, dryness of eyes, dyspepsia, eye debris, eye discharge, eye pain, eye tearing, eyelid edema, eyelid erythema, eyelid exudates/scales, eyelid pain or discomfort, foreign body sensation, glaucomatous cupping, headache, hypertension, influenza, lens nucleus coloration, lens opacity, nausea, nuclear lens opacity, pharyngitis, post-subcapsular cataract, sinusitis, upper respiratory infection, urinary tract infection, visual field defect, and vitreous detachment. Other adverse reactions that have been reported with the individual components are listed below:
Dorzolamide:
2% Angioedema, asthenia/fatigue, bronchospasm, contact dermatitis, epistaxis, eyelid crusting, ocular discomfort, photophobia, signs and symptoms of ocular allergic reaction, transient myopia.
Timolol (ocular administration):
Body as a whole: Asthenia/fatigue; Cardiovascular: arrhythmia, syncope, cerebral ischernia, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema claudication, Raynaud's phenomenon, and cold hands and feet; Digestive: anorexia, abdominal pain; Immunologic: systemic lupus erythematosus; Nervous system/psychiatric: increase in signs and symptoms of myasthenia gravis, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; Skin: alopecia, psoriasis form rash or exacerbation of psoriasis; Hypersensitivity: signs and symptoms of systemic allergic reactions, including anaphylaxis, angioederna, urticaria, and localized and generalized rash; Respiratory: bronchospasm (predominantly in patients with pre-existing bronchospastic disease); Endocrine: masked symptoms of hypoglycemia in diabetic patients; Special Senses: ptosis, decreased corneal sensitivity, cystoid macular edema, visual disturbances including refractive changes and diplopia, pseudopemphigoid, and tinnitus; Urogenitial: retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease; Musculoskeletal: myalgia.

OVERDOSE AND TREATMENT:
No data are available in humans with regards to overdose by accidental or deliberate ingestion of dorzolamide 20 mg/mL and timolol 5 mg/mL eye drops solution.
Symptoms:
There have been reports of inadvertent overdoses with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm and cardiac arrest. The most common signs and symptoms to be expected with overdoses of dorzolamide are electrolyte imbalance, development of an acidotic state and possibly central nervous system effects. Only limited information is available with regard to human overdose by accidental or deliberate ingestion of dorzolamide hydrochloride. With oral ingestion, somnolence has been reported. With topical application the following have been reported: nausea, dizziness, headache, fatigue, abnormal dreams and dysphagia.
Treatment:
Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

Keep out of reach of children.

DOSAGE FORMS AND PACKAGING AVAILABLE (pack size):
Opaque Plastic Bottle with nozzle cap x 5 mL (Box of 1's)

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction."

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Manufactured by:
MAKCUR LABORATORIES LIMITED
46/4-7, Dehgam Road Village Zak, Tal-Dehgam Dist: Gandhinagar ,
Gujarat State, India

Imported by:
AFREE PHARMACEUTICAL DISTRIBUTION CORP.
239 Contemprato Apt., San Jose St., Brgy. 2,
Carmona, Cavite

Distributed by:
MEDCHOICE VISION CARE INC.
Unit 907, 88 Corporate Center, Sedeño cor. Valero Sts., Salcedo Village, Makati City, Metro Manila

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