EyeKare

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*For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory*

# Dorzoeye®-T

# DORZOLAMIDE & TIMOLOL EYE DROPS IP

**COMPOSITION**

Dorzolamide Hydrochloride IP equivalent to Dorzolamide 2.0% w/v, Timolol Maleate IP equivalent to Timolol 0.5 % w/v, Purified Water IP q.s.
Specially designed container to avoid preservative use.

**CLINICAL PHARMACOLOGY**

Mechanism of Action: Dorzoeye-T is comprised of two components: Dorzolamide HCL & Timolol Maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humour secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve and glaucomatous visual field loss. Higher the level of intraocular pressure, greater will be the likehood of glaucomatous visual field loss & optic nerve damage. Dorzolamide HCL is an 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 beta1 and beta2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilizing) activity**.** The combined effect of these two agents administered as Dorzoeye-T b.i.d results in additional intraocular pressure reduction compared to their compared to either component administered alone, but the reduction is not as much as when Dorzolamide t.i.d. and Timolol b.i.d. are administered concomitantly**.**

**Pharmacokinetics / Pharmacodynamics**

Dorzolamide HCL : When topically applied , Dorzolamide reaches the systemic circulation **.** To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than parent drug but also inhibits CA-I.The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of Dorzolamide and metabolite are generally below the assay limit of quantification (15nM). Dorzolamide binds moderately to plasma proteins (approx. 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, Dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half–life of about four months.

To stimulate the systemic exposure after long – term ocular administration, Dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg. b.i.d. closely approximates the amount of drug delivered by topical ocular administration of Dorzolamide 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of CA-II & total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function in healthy individuals.

**Timolol Maleate:** In a study of plasma drug concentrations in six subjects, the systemic exposure to Timolol was determined following twice daily topical administration to Timolol Maleate ophthalmic solution 0.5 %. The mean peak plasma concentration following morning dosing was 0.46 ng/mL.

**INDICATIONS AND USES:** Dorzoeye-T is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It has additive value in patients who are insufficiently responsive to beta – blockers and in patients were the desire target pressure are difficult to achieve with a single drug.

**CONTRAINDICATIONS:** Dorzoeye-T is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma ; (3) sever chronic obstructive pulmonary disease ; (4) sinus bradycardia ; (5) second or third degree atrioventricular block; (6) overt cardiac failure ; (7) cardiogenic shock ; or (8) hypersensitivity to any component of this product.

**WARNINGS**

**Systemic Exposure:** Dorzoeye-T contains Dorzolamide, a sulfonamide and Timolol maleate, a beta **-** adrenergic blocking agent and although administered topically, is absorbed systemically**.** Therefore, the same type of adverse relations that are attributable to sulfonamides and/or systemic administration of beta- adrenergic agents may occur with topical administration. For example. Severe respiratory reactions & cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate. Fatalities have occurred, although rarely, due to severe reactions of sulphonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia & other blood dyscrasias. Sensitization may occur when a sulphonamide is re- administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

**PRECAUTIONS:**

General: Dorzolamide has not been studied in patients with severe renal impairment, because Dorzolamide & its metabolites are execreted predominantly by the kidney, Dorzoeye-T is not recommended in such patients. Dorzolamide has been studied in patients with hepatic impairment and should therefore be used with caution in such patients. While taking beta-blockers patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be reactive to repeated accidental, diagnostic, or therapeutic challenges with such allergens. Such patients may be unresponsive to the usual doses of epinephrine use to treat anaphylactic reactions. The management of patients with acute angle closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzoeye-T has not been studied in patients with acute angle closure glaucoma. Choroidal detachment after filtration procedure has been reported with the administration of aqueous suppressant therapy (e.g. , Timolol). Beta adrenergic blocked has been reported potentate muscles weakness consistent with certain myasthenia symptoms (e.g., Diplopia, Ptosis, generalise weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms. There have been reports of bacterial keratitis associated with the use of multiple dose container of topical ophthalmic products. This container had been inadvertently contaminated by patient who, in most cases, had a concurrent corneal disease or in a disruption of the corneal epithelial surface. Patient should be advice that if they develop any ocular relations, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician advice. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Contact lenses should be remove prior to administrations of the solution. Lenses may be reinserted 15 min. following administration of Dorzoeye-T **.**

**Pregnancy : Teratogenic effects. Pregnancy category C .** Developmental toxicity studied with the Dorzolamide HCL. In rabits at oral doses of = 2.5 mg / kg / day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that cause metabolic acidosis with decreased body weight & decrease fetal weights. No treatments – related malformations were seen at 1.0 mg / kg / day (13 times the recommended human ophthalmic dose). Teratogenicity studies with timolol on mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommends human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at these dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg / kg / day (142,000 times the systemic exposure following the maximum recommends human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorption were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well controlled studies in pregnant woman. Dorzoeye – T should be use during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Nusing Mothers :** It is not known whether Dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Dorzoeye-T in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into accounts of the drug to the mother**.**

**Paediatric Use:** Safety and effectiveness paediatric patients have not been established.

**Geriatric Use :** No overall differences in safety or effectiveness have been observe between elderly and younger patients.

**ADVERSE REACTIONS:** Adverse reactions that have been reported with the individual components are listed below:

*Dorzolamide- Allergic/hypersensitivity*: Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, pruritus, urticaria; Body as whole: asthenia/ fatigue; skin/ mucus membrane : contact dermatitis ; epistaxis; throat irritation;

**Special senses:** Eyelid crusting, signs and symptoms of ocular allergic reactions and transient myopia.

Timolol (ocular administration) **-** Body as whole : asthenia/fatigue; cardiovascular: arrhythmia, syncope, heart block , cerebral ischemia, worsening of anginapectorios, palpitation, cardiac arrest, pulmonary edema, edema , claudication, Raynaud's phenomenon, and cold hands and feet; digestive : anorexia; immunologic: systemic lupus erythematosus; nerves system / psychiatric: increase in sign and symptoms of myasthenia gravis, somnolence, insomnia, nightmares, behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation , nervousness and memory loss; skin: alopecia, psoriasiform, rash or exacerbation of psoriasis; hypersensitivity : Sign and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticarial, localised and generalised rash ; respiratory : bronchospasm ( predominantly in patients with pre-existing branchospastic disease): endocrine ; masked symptoms of hypoglycaemia in diabetic patients ( see warnings);

**Special senses:** Ptosis; decrease cornea sensitivity; cystoid macula edema; visual disturbances including refractive changes and diplopia; psudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, generals); and tinnitus ; urogenital: retroperitoneal fibrosis, decrease libido , impotence and peyronie's disease. The following additional adverse effect have been reported in clinical experience with oral.

Timolol maleate or other oral beta blocking agents and may be considered potential effects of ophthalmic timolol maleate; *allergic* ; erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; body as whole : extremity pain , decreased exercise tolerance, weight loss ; Cardiovascular ; worsening of arterial insufficiency , vasodilation ; digestive : gastrointestinal pain, hepatomegaly, mesenteric, arterial thrombosis , ischemic colitis , hematologic; nonthrombocytopenic purpura ; thrombocytopenic purpura, agranulocytosis;

Endocrine: hyperglycaemia , hypoglycaemia; skin; pruritus, skin irritation, increased pigmentation, sweating ; musculoskeletal; arthralgia; nervous system/ psychiatric ; vertigo , local weakness diminished concentration, reversible mental depression progressing to catatonia , an acute reversible syndrome characterised by disorientation for time and place , emotional lability , slightly clouded sensorium and decreased performance on euro psychometrics;

Respiratory: Rales, bronchial obstruction; urogenital ; urination difficulties.

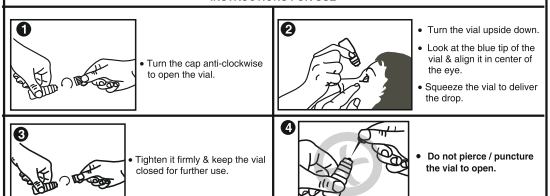
**OVERDOSAGE:** There are no human data available on overdoses with Dorzoeye -T**.**

**DOSAGES AND ADMINISTRATION:** The recommended dose is one drop of DORZOEYE T in the affected eye(s) 2 times daily**.**

**STORAGE CONDITION: Store at a temperature not exceeding 30°C and protect from light.** Keep out of reach of children.
Use the solution within 60 days after opening the container
For external use only**.**

**PACK AND PRESERVATION:** Dorzoeye-T is available as a sterile solution in 10 ml bottle.

**INSTRUCTIONS FOR USE**

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