

# **DORZOX-T Eye Drops (Dorzolamide hydrochloride 2% + Timolol maleate 0.5%)**

## **Composition**

Each ml contains:

Dorzolamide Hydrochloride, USP

equivalent to Dorzolamide ..... 2% w/v

Timolol Maleate, IP, equivalent to Timolol ..... 0.5% w/v

Benzalkonium Chloride, NF ..... 0.0075% w/v  
(as preservative)

Aqueous vehicle ..... q.s.

## **Dosage Form**

Ophthalmic solution

## **Description**

**DORZOX-T** eye drops (dorzolamide hydrochloride-timolol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

## **Pharmacology**

### **Pharmacodynamics**

#### ***Mechanism of action***

**DORZOX-T** is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure (IOP), whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated IOP is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase-II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a beta<sub>1</sub> and beta<sub>2</sub> (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 dorzolamide-timolol fixed dose combination twice daily results in additional IOP reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide three times daily and timolol twice daily are administered concomitantly.

This medicinal product reduces IOP without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

### ***Clinical Studies in Adults***

Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect over the course of the day of Dorzolamide-Timolol fixed dose combination twice daily (dosed morning and bed-time) to individually and concomitantly administered 0.5% timolol twice daily and 2% dorzolamide twice and three times daily. The IOP-lowering effect of Dorzolamide-Timolol fixed dose combination twice daily was greater (1 to 3 mmHg) than that of monotherapy with either 2% dorzolamide three times daily or 0.5% timolol twice daily. The IOP-lowering effect of Dorzolamide-Timolol fixed dose combination twice daily was approximately 1 mmHg less than that of concomitant therapy with 2% dorzolamide three times daily and 0.5% timolol twice daily. Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of Dorzolamide-Timolol fixed dose combination twice daily was consistent during the 12-month follow-up period.

### ***Clinical Studies in Paediatric Population***

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 and greater than or equal to 2 years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received Dorzolamide-Timolol fixed dose combination in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Dorzolamide-Timolol fixed dose combination 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***

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 the red blood cells (RBCs) and plasma and carbonic anhydrase inhibition in the RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to carbonic anhydrase-II while extremely low concentrations of free active substance in plasma are maintained. The parent drug forms a single N-desethyl metabolite, which not only inhibits carbonic anhydrase-II less potently than the parent drug but also inhibits carbonic anhydrase-I. The metabolite also accumulates in the RBCs where it binds primarily to carbonic anhydrase-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of the 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 simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg twice daily closely approximates the amount of drug delivered by topical ocular administration of dorzolamide ophthalmic solution 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of carbonic

anhydrase-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration 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 of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing, it was 0.35 ng/ml.

## **Indications**

Dorzolamide-Timolol fixed dose combination ophthalmic solution is indicated for the reduction of elevated IOP in patients with open-angle glaucoma, or ocular hypertension, who are insufficiently responsive to beta-blockers (failed to achieve the target IOP determined after multiple measurements over time).

The IOP-lowering of Dorzolamide-Timolol fixed dose combination administered twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol administered twice a day and 2% dorzolamide administered three times a day.

## **Dosage and Administration**

The dose is one drop of Dorzolamide-Timolol fixed dose combination in the affected eye(s) two times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

## **Contraindications**

### **Asthma, COPD**

Dorzolamide-Timolol fixed dose combination is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.

### **Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock**

Dorzolamide-Timolol fixed dose combination is contraindicated in patients with sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, and cardiogenic shock.

### **Hypersensitivity**

Dorzolamide-Timolol fixed dose combination is contraindicated in patients who are hypersensitive to any component of this product.

### **Renal Impairment**

Dorzolamide-Timolol fixed dose combination is contraindicated in severe renal impairment (CrCl < 30 ml/min) or hyperchloraemic acidosis.

# Warnings and Precautions

## General

DORZOX T ophthalmic solution contains timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. Therefore, the same types of cardiovascular, pulmonary and adverse reactions that are attributable to systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory 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. Incidence of systemic adverse drug reactions after topical ophthalmic administration is lower than for systemic administration.

Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with this medicinal product. If such reactions occur, discontinuation of this medicinal product should be considered.

## Cardiac Failure

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 failure.

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, Dorzolamide-Timolol fixed dose combination should be discontinued.

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

## Sulfonamide Hypersensitivity

**DORZOX-T** ophthalmic solution contains dorzolamide, a sulfonamide; and although administered topically, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of this product. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

## Obstructive Pulmonary Diseases

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 dorzolamide-timolol fixed dose combination ophthalmic solution is contraindicated) should, in general, not receive beta-blocking

agents, including dorzolamide-timolol fixed dose combination.

## **Increased Reactivity to Allergens**

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

## **Potentialiation 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.

## **Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus**

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycaemia.

## **Masking of 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.

## **Renal and Hepatic Impairment**

Dorzolamide has not been studied in patients with severe renal impairment (CrCl <30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidneys, Dorzolamide-timolol fixed dose combination ophthalmic solution is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should, therefore, be used with caution in such patients.

## **Impairment of Beta-Adrenergically Mediated Reflexes During 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 anaesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anaesthesia. 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 blocking agents may be reversed by sufficient doses of adrenergic agonists.

## **Corneal Endothelium**

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 Dorzolamide-Timolol fixed dose combination to this group of patients.

## **Surgical Anaesthesia**

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

## **Bacterial Keratitis**

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 ocular epithelial surface.

## **Vascular Disorders**

Patients with severe peripheral circulatory disturbance/disorders (e.g., severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

## **Concomitant Therapy**

The effect on intraocular pressure or the known effects of systemic beta blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.

The use of dorzolamide and oral carbonic anhydrase inhibitors is not recommended.

## **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**

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

## **Additional Effects of Carbonic Anhydrase Inhibition**

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 **DORZOX T** ophthalmic solution 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.

## **Other**

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide-timolol fixed dose combination ophthalmic solution has not been studied in patients with acute angle-closure glaucoma.

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing **DORZOX T** ophthalmic solution to these groups of patients.

Choroidal detachment has been reported with the administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

As with the use of other antiglaucoma medicines, diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

## **Contact Lens Use**

This medicinal product contains the preservative benzalkonium chloride, which may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

## **Effects on Ability to Drive and Use Machines**

No studies on the effects on the ability to drive and use machines have been performed. Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery.

## **Drug Interactions**

Specific medicine interaction studies have not been performed with **DORZOX T** ophthalmic solution.

In clinical studies, Dorzolamide-Timolol fixed dose combination was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

### ***Oral Carbonic Anhydrase Inhibitors***

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and Dorzolamide-timolol fixed dose combination. The concomitant administration of Dorzolamide-timolol fixed dose combination and oral carbonic anhydrase inhibitors is not recommended.

### ***High-Dose Salicylate Therapy***

Although acid-base and electrolyte disturbances were not reported in the clinical trials with

dorzolamide hydrochloride ophthalmic solution, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g. toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving Dorzolamide-timolol fixed dose combination.

### ***Beta-Adrenergic Blocking Agents***

Patients who are receiving a beta-adrenergic blocking agent orally and Dorzolamide-timolol fixed dose combination should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

### ***Calcium Antagonists***

Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Dorzolamide-timolol fixed dose combination and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

### ***Catecholamine-Depleting Drugs***

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope or postural hypotension.

### ***Digitalis and Calcium Antagonists***

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

### ***CYP2D6 Inhibitors***

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.

### ***Clonidine***

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

### ***Others***

Although dorzolamide hydrochloride-timolol maleate fixed dose combination alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic timolol maleate and epinephrine (adrenaline) has been reported occasionally.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.

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.

## **Pregnancy**

### ***Teratogenic Effects***

#### *Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. Dorzolamide-timolol fixed dose combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Lactation

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 Dorzolamide-Timolol fixed dose combination in nursing infants, a decision should be made whether to discontinue lactation or to discontinue the drug, taking into account the importance of the drug to the mother.

## **Paediatric Use**

The safety and effectiveness of dorzolamide hydrochloride ophthalmic solution and timolol maleate ophthalmic solution have been established when administered individually in paediatric patients aged 2 years and older. Use of these drug products in these children is supported by evidence from adequate and well-controlled studies in children and adults.

Safety and efficacy in paediatric patients below the age of 2 years have not been established.

## **Geriatric Use**

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

## **Undesirable Effects**

### **Clinical Studies Experience**

Because 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-angle-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 oedema, 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 oedema, eyelid erythema, eyelid exudates/scales, eyelid pain or discomfort, foreign body sensation, glaucomatous cupping, headache, hypertension, influenza, lens nucleus colouration, 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 ischemia, 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, psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, 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; *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease; *Musculoskeletal:* Myalgia.

### **Post-Marketing Experience**

The following adverse reactions have been identified during post-approval use of Dorzolamide-Timolol fixed dose combination. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: bradycardia, cardiac failure, cerebral vascular accident, chest pain, choroidal detachment following filtration surgery, depression, diarrhoea, dry mouth, dyspnoea, heart block, hypotension, iridocyclitis, myocardial infarction, nasal congestion, Stevens-Johnson syndrome, toxic epidermal necrolysis, paraesthesia, photophobia, respiratory failure, skin rashes, urolithiasis, and vomiting.

### **Timolol (oral administration)**

The following additional adverse reactions 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 a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *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 characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory*: Rales, bronchial obstruction; *Urogenital*: Urination difficulties.

The following adverse reactions have been reported with Dorzolamide-Timolol fixed dose combination or one of its components either during clinical trials or during post-marketing experience: [Very Common: ( $\geq 1/10$ ), Common: ( $\geq 1/100$  to  $<1/10$ ), Uncommon: ( $\geq 1/1000$  to  $<1/100$ ), and Rare: ( $\geq 1/10,000$  to  $<1/1000$ ), Not known (cannot be estimated from the available data)]

System Organ Class (MedDRA)	Formulation	Very Common	Common	Uncommon	Rare	Not Known**
Immune system disorders	Dorzolamide-Timolol fixed dose combination				signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis	
	Timolol maleate eye drops, solution				Signs and symptoms of allergic reactions including angioedema, urticaria, localised and generalised rash, anaphylaxis	pruritus
Metabolism and nutrition disorders	Timolol maleate eye drops, solution					Hypoglycaemia
Psychiatric disorders	Timolol maleate eye drops, solution			Depression*	insomnia*, nightmares*, memory loss	
Nervous system disorders	Dorzolamide hydrochloride eye drops, solution		headache*		dizziness*, paraesthesia*	
	Timolol maleate eye drops, solution		headache*	dizziness*, syncope*	paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*, cerebral ischaemia	

Eye disorders	Dorzolamide-Timolol fixed dose combination	Burning and stinging	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing			
	Dorzolamide hydrochloride eye drops, solution		eyelid inflammation*, eyelid irritation*	iritidocyclitis*	irritation including redness*, pain*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal detachment (following filtration surgery)*	
	Timolol maleate eye drops, solution		signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal	visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*	ptosis, diplopia, choroidal detachment following filtration surgery*	itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders	Timolol maleate eye drops, solution				tinnitus*	
Cardiac disorders	Timolol maleate eye drops, solution			Bradycardia*	chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block	atrioventricular block, cardiac failure
Vascular disorders	Timolol maleate eye drops, solution				hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*	
Respiratory, thoracic, and mediastinal disorders	Dorzolamide-Timolol fixed dose combination		sinusitis		shortness of breath, respiratory failure, rhinitis, rarely bronchospasm	
	Dorzolamide hydrochloride eye drops, solution				epistaxis*	

	Timolol maleate eye drops, solution			dyspnoea*	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*	
Gastrointestinal disorders	Dorzolamide-Timolol fixed dose combination	dysgeusia				
	Dorzolamide hydrochloride eye drops, solution		nausea*		throat irritation, dry mouth*	
	Timolol maleate eye drops, solution			nausea*, dyspepsia*	diarrhoea, dry mouth*	dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	Dorzolamide-Timolol fixed dose combination				contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	
	Dorzolamide hydrochloride eye drops, solution				Rash*	
	Timolol maleate eye drops, solution				Alopecia*, psoriasiform rash or exacerbation of psoriasis*	Skin rash
Musculoskeletal and connective tissue disorders	Timolol maleate eye drops, solution				systemic lupus erythematosus	myalgia
Renal and urinary disorders	Dorzolamide-Timolol fixed dose combination			urolithiasis		
Reproductive system and breast disorders	Timolol maleate eye drops, solution				Peyronie's disease*, decreased libido	Sexual dysfunction
General disorders and administration site conditions	Dorzolamide hydrochloride eye drops, solution		asthenia/fatigue*			
	Timolol maleate eye drops, solution			asthenia/fatigue*		

\*These adverse reactions were also observed with dorzolamide-timolol fixed dose combination during post-marketing experience.

\*\*Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with dorzolamide-timolol fixed dose combination.

If you experience any side effects, talk to your doctor or pharmacist or write to [drugsafety@cipla.com](mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance

program of India by calling on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

## Overdosage

No data are available in humans regarding overdose by accidental or deliberate ingestion of dorzolamide-timolol fixed dose combination.

Symptoms consistent with systemic administration of beta-blockers or carbonic anhydrase inhibitors may occur, including electrolyte imbalance, development of an acidotic state, dizziness and headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest, and possible central nervous system effects.

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. A study of patients with renal failure showed that timolol did not dialyze readily.

## Incompatibility

No data available.

## Shelf-Life

2 years

## Storage and Handling Instructions

Store in a cool, dry place. Protect from light.

## Packaging Information

**DORZOX-T Eye Drops:** Vial of 5 ml

## Information for Patients

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block or cardiac failure should be advised not to take this product.

**DORZOX-T** ophthalmic solution contains dorzolamide (which is a sulphonamide) and, although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulphonamides may occur with topical administration, including severe skin reactions. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the dispensing container to contact the eyes or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eyes or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eyes and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g. trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multi-dose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Patients should be advised that Dorzolamide-Timolol fixed dose combination ophthalmic solution contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted after 15 minutes following administration of Dorzolamide-timolol fixed dose combination.

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