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

Dorzolamide Hydrochloride and Timolol Maleate
Ophthalmic Solution USP 2.0 %w/v & 0.5% w/v

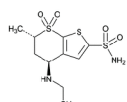
DORSENZ®-T

For the use of Registered Medical Practitioner only

Composition

Dorzolamide Hydrochloride USP equivalent to Dorzolamide ..... 2.0% w/v
Timolol Maleate USPequivalent to Timolol .....0.5% w/v
Benzalkonium Chloride Solution USP ..... 0.02% v/v
(as preservative)
Water for Injection USP ..... q.s.

Chemical Structure & Name



D

$C_{10}H_{16}N_2O_4S_3 \bullet HCl$

4*H* -Thieno[2, 3-*b*]thiopyran – 2 - sulfonamide, 4 - (ethylamino) - 5, 6 – dihydro – 6 – methyl -, 7, 7 - dioxide, monohydrochloride, (*4S – trans*) - .

(4*S* , 6*S*) – 4 - (Ethylamino) - 5, 6 – dihydro - 6 - methyl-4*H* – thieno [2, 3-*b*] thiopyran – 2 - sulfonamide 7, 7 - dioxide, monohydrochloride

Timolol Maleate

$C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$

2-Propanol, 1-(1,1-dimethylethyl)amino-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-, (*S*)-, (*Z*)-2-butenedioate (1:1) (salt).

(-)-1-(tert-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt)

Category

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations

ATC code: S01ED51

Description

Ophthalmic Solution.

A clear, colourless solution free from visible particles is packed in 5 mL White Opaque LDPE Bottles with natural, transparent open LDPE Nozzle and white HDPE tamp safe caps

Pharmacology

Each of the two components of Dorzolamide Hydrochloride and Timolol Maleate

Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v decreases the elevated intraocular 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 intraocular pressure is not clearly established, 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 intraocular pressure reduction (IOP) compared to either component administered alone.

Following topical administration, this medicinal product reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. This medicinal product reduces intra-ocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Pharmacokinetic

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. Dorzolamide

accumulates in RBCs during chronic dosing as a result of selective binding 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 washes 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 that 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 Hydrochloride and Timolol Maleate Ophthalmic Solution 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 & Administration

The dose is one drop of Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v in the (conjunctival sac of the) affected eye(s) two times daily.

If another topical ophthalmic agent is being used, Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v and the other agent should be administered at least ten minutes apart.

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.

Method of Administration

1. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and eye.
2. Invert the bottle, and press lightly with the thumb or index finger until a single drop is dispensed into the eye as directed by your doctor. Do not touch your eye or eyelid with the dropper tip.
3. 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.
4. The dispenser tip is designed to provide a single drop; therefore, do not enlarge the hole of the dispenser tip.
5. After you have used all doses, there will be some medicine left in the bottle. You should not be concerned since an extra amount of medicine has been added and you will get the full amount of Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v that your doctor prescribed. Do not attempt to remove the excess medicine from the bottle.

Paediatric population

Efficacy in paediatric patients has not been established. Safety in paediatric patients below the age of 2 years has not been established.

Contraindications

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5% w/v is contraindicated in patients with:

- Reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- 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 < 0.5 mL/s) or hyperchloraemic acidosis
- Hypersensitivity to one or both active substances or to any of the excipients.

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

Warning and Precaution

Cardiac Disorders

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.

Vascular Disorders

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

Respiratory Disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5 % w/v should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hepatic Impairment

This medicinal product has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Immunology and Hypersensitivity

As with other topically-applied ophthalmic agents, this medicinal product may be absorbed systemically. Dorzolamide contains a sulfonamido group, which

also occurs in sulphonamides. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation. 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.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Concomitant Therapy

The effect on intra-ocular 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 betaadrenergic 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.

Additional Effects of Beta-Blockers

Hypoglycaemia/diabetes: Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia. Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms

Corneal diseases

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

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.

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 Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v 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. This medicinal product has not been studied in patients with acute angle-closure glaucoma. Corneal oedema and irreversible cornealdecompensation 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 Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v to these groups of patients. Choroidal detachment has been reported with

administration of aqueous suppressant therapies (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.

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.

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 Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons. 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.

Interactions

Specific medicine interaction studies have not been performed with Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v. In clinical studies, this medicinal product 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).

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) andtimolol. Acid-base 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 Hydrochloride and Timolol Maleate

Ophthalmic Solution

Although Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v 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 hypoglycaemic effect of antidiabetic agents. Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Pregnancy & Lactation

Pregnancy

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v should not be used during pregnancy.

Dorzolamide: No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effect at maternotoxic doses.

Timolol: There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. Epidemiological studies have not revealed malformative effects but show a risk

for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If this medicinal product is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

It is not known whether dorzolamide is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed. Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of betablockade in the infant.

If treatment with Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v is required, then lactation is not recommended.

Adverse reaction

In clinical studies for Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5 % w/v the observed adverse reactions have been consistent with those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. Like other topically applied ophthalmic medicines, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

The following adverse reactions have been reported with Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.00 % w/v & 0.5 % w/v and either Dorzolamide Hydrochloride or Timolol Maleate during clinical trials or during post-marketing experience: [Very Common: (≥ 1/10), Common: (≥ 1/100 to <1/10), Uncommon: ≥ 1/1000 to <1/100), and Rare: (≥ 1/10,000 to <1/1000), Not known (cannot be estimated from the available data)]

Immune system disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution Rare: signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis

Metabolism and nutrition disorders

Timolol maleate ophthalmic solution:

Not known**: hypoglycaemia

Psychiatric disorders

Timolol maleate eye drops, solution

Uncommon: depression*

Rare: insomnia*, nightmares*

Nervous system disorders

Dorzolamide hydrochloride eye drops, solution

Common: headache*

Rare: dizziness*, paraesthesia*

Timolol maleate eye drops, solution

Common: headache*

Uncommon: dizziness*, syncope*

Rare: paraesthesia*, cerebrovascular accident*

Eye disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Very common: burning and stinging

Common: conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing

Not known: foreign body sensation in eye

Dorzolamide hydrochloride eye drops, solution

Common: eyelid inflammation*, eyelid irritation*

Uncommon: iridocyclitis*

Rare: irritation including redness*, pain*, eyelid crusting*, corneal oedema*, ocular hypotony*, choroidal detachment (following filtration surgery)*

Timolol maleate eye drops, solution

Common: signs & symptoms of ocular irritation including blepharitis*, keratitis*, and dry eyes*

Uncommon: visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*

Rare: choroidal detachment following filtration surgery*

Ear and labyrinth disorders

Timolol maleate eye drops, solution

Rare: tinnitus*

Cardiac disorders

Timolol maleate eye drops, solution

Uncommon: bradycardia*

Rare: chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest* Not Known**: atrioventricular block, cardiac failure

Vascular disorders

Timolol maleate eye drops, solution

Rare: hypotension*, Raynaud's phenomenon*, cold hands and feet*

Respiratory, thoracic, and mediastinal disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Common: sinusitis

Rare: shortness of breath, respiratory failure, rhinitis, rarely bronchospasm

Dorzolamide hydrochloride eye drops, solution

Rare: epistaxis*

Timolol maleate eye drops, solution

Uncommon: dyspnoea*

Rare: bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*,
respiratory failure, cough*

Gastrointestinal disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Very Common: dysgeusia

Dorzolamide hydrochloride eye drops, solution

Common: nausea*

Rare: dry mouth*

Timolol maleate eye drops, solution

Uncommon: nausea*, dyspepsia*

Rare: dry mouth*

Not known**: abdominal pain, vomiting

Skin and subcutaneous tissue disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Rare: contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dorzolamide hydrochloride eye drops, solution

Rare: rash*

Timolol maleate eye drops, solution

Rare: alopecia*, psoriasiform rash or exacerbation of psoriasis*

Not known**: Pruritus, skin rash

Renal and urinary disorders

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Uncommon: urolithiasis

Reproductive system and breast disorders

Timolol maleate eye drops, solution

Rare: Peyronie's disease*, decreased libido*

Not known**: sexual dysfunction

General disorders and administration site conditions

Dorzolamide hydrochloride eye drops, solution
Common: asthenia/ fatigue*
Timolol maleate eye drops, solution
Uncommon: asthenia/ fatigue*
Musculoskeletal and connective tissue disorders
Not known**: myalgia
*These adverse reactions were also observed with Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5 % w/v during post-marketing experience.
**Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5 % w/v.

Overdosage

No data are available in humans in regard to overdose by accidental or deliberate ingestion of Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution USP 2.0 % w/v & 0.5 % w/v.

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, and 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 notdialyse readily.

Storage

Store between 15°C - 30 °C. Protect from light
Keep out of reach of children.

Shelf life

24 Months from the date of manufacture.

Presentation

A clear colourless solution filled in 5mL Sterile Gamma-irradiated white opaque LDPE bottle sealed with Sterile Gamma-irradiated natural transparent LDPE open nozzle and Sterile Gamma-irradiated white HDPE tamp safe cap in printed carton along with leaflet.

Directions for use :

Turn the tamper proof cap anti-clockwise to break the seal.

Remove the cap, dispense drops with gentle pressure.

Replace the cap immediately after every use.

Manufactured in INDIA by :
Senses Pharmaceuticals Pvt. Ltd.,
No.77, 3rd Road, Bommasandra Industrial Area,
Bommasandra 4th Phase, Bengaluru - 560 099.
Email: info@sensespharma.com

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Month of publication of pack insert: June 2023