Brimonidine Tartrate and Timolol Maleate Eye Drops 0.2 % w/v & 0.5 % w/v

DUOBRIM® – T

For the use of Registered Medical Practitioner only

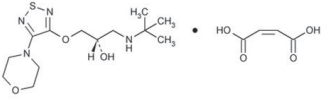
Composition

Brimonidine Tartrate BP ..... 0.2% w/v
Timolol Maleate USP equivalent 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
Brimonidine Tartrate

C11H10BrN5· C4H6O6
Brimonidine: 5-bromo-*N*-(4,5-dihydro-1H-imidazol-2-yl) quinoxalin-6-amine

Timolol Maleate



C13H24N4O3S • C4H4O4
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).

Category

Pharmacotherapeutic group: Ophthalmological – antiglaucoma preparations and miotics - beta-blocking agents – timolol, combinations
ATC code: S01ED51

Description

A Clear greenish yellow colour solution packed 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.

Pharmacology

Brimonidine Tartrate and Timolol Maleate Eye Drops consists of two active substances: brimonidine tartrate and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

Brimonidine Tartrate and Timolol Maleate Eye Drops have a rapid onset of action. Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor. This selectivity results in no mydriasis and the absence of

vasoconstriction in micro vessels associated with human retinal xenografts. It is thought that brimonidine tartrate lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation.

Timolol 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-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation.

The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

In addition, the IOP-lowering effect of Brimonidine Tartrate and Timolol Maleate Eye Drops was consistently non-inferior to that achieved by adjunctive therapy of brimonidine and timolol (all twice daily).

The IOP-lowering effect of Brimonidine Tartrate and Timolol Maleate Eye Drops has been shown to be maintained in double-masked studies of up to 12 months.

Pharmacokinetic:

Brimonidine Tartrate and Timolol Maleate Eye Drops

Plasma brimonidine and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to Brimonidine Tartrate and Timolol Maleate Eye Drops treatment in healthy subjects. There were no statistically significant differences in brimonidine or timolol AUC between Brimonidine Tartrate and Timolol Maleate Eye Drops and the respective monotherapy treatments. Mean plasma Cmaxvalues for brimonidine and timolol following dosing with Brimonidine Tartrate and Timolol Maleate Eye Drops were 0.0327 and 0.406 ng/ml respectively.

Brimonidine

After ocular administration of 0.2% eye drops solution in humans, plasma brimonidine concentrations are low. Brimonidine is not extensively metabolised in the human eye and human plasma protein binding is approximately 29%. The mean apparent half-life in the systemic circulation was approximately 3 hours after topical dosing in man. Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 74% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism. Brimonidine binds extensively and reversibly to melanin in ocular tissues without any untoward effects. Accumulation does not occur in the absence of melanin. Brimonidine is not metabolised to a great extent in human eyes.

Timolol

After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour postdose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 7 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma protein.

Indications

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

Dosage & Administration

Paediatric population

Brimonidine Tartrate and Timolol Maleate Eye Drops is contraindicated in neonates andinfants (less than 2 years of age).

The safety and effectiveness of Brimonidine Tartrate and Timolol Maleate Eye Drops in children and adolescents (2 to 17 years of age) have not been

established and therefore, its use is not recommended in children or adolescents.

Recommended dosage in adults (including the elderly)

The recommended dose is one drop of Brimonidine Tartrate and Timolol Maleate Eye Drops in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

Method of Administration:

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctual occlusion) or eyelids are closed for two minutes. This should be performed immediately following the instillation of each drop. This may result in a decrease of systemic side effects and an increase in local activity.

To avoid contamination of the eye or eye drops do not allow the dropper tip to come into contact with any surface.

Use in renal and hepatic impairment

Brimonidine Tartrate and Timolol Maleate Eye Drops have not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients.

Contraindications

- Hypersensitivity to the active substances or to any of the excipients.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not controlled with a pace-maker, overt cardiac failure, cardiogenic shock.
- Use in neonates and infants (less than 2 years of age).
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

Warning and Precaution

Paediatric population

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing $\leqslant$ 20 kg should be treated with caution and closely monitored due to the high incidence and severity of somnolence. The safety and effectiveness of Brimonidine Tartrate and Timolol Maleate Eye Drops in children and adolescents (2 to 17 years of age) have not been established.

Some patients have experienced ocular allergic type reactions (allergic conjunctivitis and allergicblepharitis) with Brimonidine Tartrate and Timolol Maleate Eye Drops in clinical trials. Allergic conjunctivitis was seen in 5.2% of patients. Onset was typically between 3 and 9 months resulting in an overall discontinuation rate of 3.1%. Allergic blepharitis was uncommonly reported (<1%). If allergic reactions are observed, treatment with Brimonidine Tartrate and Timolol Maleate Eye Drops should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solution 0.2%, with some reported to be associated with an increase in Intra ocular pressure.

Like other topically applied ophthalmic agents, Brimonidine Tartrate and Timolol Maleate Eye Drops may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Cardiac disorders

Cardiac reactions have been reported including, rarely, death associated with cardiac failure following administration of timolol. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with betablockers 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.
As with systemic beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarct or sudden death.

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.
Brimonidine Tartrate and Timolol Maleate Eye Drops 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.

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.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.
Brimonidine Tartrate and Timolol Maleate Eye Drops must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

Corneal diseases

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

Other beta-blocking agents

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.

Anaphylactic reactions

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 allergans and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

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

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthetist must be informed if the patient is receiving timolol. The preservative in Brimonidine Tartrate and Timolol Maleate Eye Drops, benzalkonium chloride, 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. Avoid contact with soft contact lenses.
Brimonidine Tartrate and Timolol Maleate Eye Drops have not been studied in patients with closed-angle glaucoma.
Brimonidine Tartrate and Timolol Maleate Eye Drops have minor influence on the ability to drive and use machines. Brimonidine Tartrate and Timolol Maleate Eye Drops may cause transient blurring of vision, visual

disturbance, fatigue and/or drowsiness which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared before driving or using machinery.

Interactions

No interaction studies have been performed with the brimonidinetimolol fixed combination. Although specific drug interactions studies have not been conducted with Brimonidine Tartrate and Timolol Maleate Eye Drops, the theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. 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, beta-adrenergic blocking agents, anti-arrhythmics (including amiodarone), digitalis glycosides, para-sympathomimetics or guanethidine. Also, after the application of brimonidine, very rare (<1 in 10,000) cases of hypotension have been reported. Caution is therefore advised when using Brimonidine Tartrate and Timolol Maleate Eye Drops with systemicantihypertensives. 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. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

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.

Concomitant use of a beta-blocker with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension, and therefore the anaesthetist must be informed if the patient is using Brimonidine Tartrate and Timolol Maleate Eye Drops.

Caution must be exercised if Brimonidine Tartrate and Timolol Maleate Eye Drops are used concomitantly with iodine contrast products or intravenously administered lidocaine. Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol. No data on the level of circulating catecholamines after Brimonidine Tartrate and Timolol Maleate Eye Drops administration are available. Caution, however, is advised in patients taking medication which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

Although specific drug interactions studies have not been conducted with Brimonidine Tartrate and Timolol Maleate Eye Drops, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect nor-adrenergic transmission (e.g. tricyclic antidepressants and miaserin). Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with Brimonidine Tartrate and Timolol Maleate Eye Drops.

Pregnancy & Lactation

There are no adequate data for the use of the brimonidinetimolol fixed combination as well as single agents in pregnant women. Brimonidine Tartrate and Timolol Maleate Eye Drops should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but have shown 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 Brimonidine Tartrate and Timolol Maleate Eye Drops are administered in pregnancy up to the time of delivery, the neonate should be carefullymonitored during the first days of life.

Breast-feeding

It is not known if brimonidine is excreted in human milk but it is excreted in the milk of the lactating rat. 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 beta-blockade in the infant. Brimonidine Tartrate and Timolol Maleate Eye Drops should not be used by women breast-feeding infants.

Adverse reaction

The most commonly reported adverse drug reactions were conjunctivalhyperaemia
(approximately 15%of patients) and burning sensation in the eye (approximately 11% of patients). The majority of these cases was mild and led to discontinuation rates of only 3.4% and 0.5% respectively.

The following adverse drug reactions were reported during clinical trials with Brimonidine Tartrate and Timolol Maleate Eye Drops:

(Frequencies are defined as: Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1000, <1/100))

Eye disorders

Very Common: conjunctivalhyperaemia, burning sensation

Common: stinging sensation in the eye, allergic conjunctivitis, corneal erosion, superficial punctuate keratitis, eye pruritus, conjunctivalfolliculosis, visual disturbance, blepharitis, epiphora, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation

Uncommon: visual acuity worsened, conjunctivaloedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment

Psychiatric disorders

Common: depression

Nervous system disorders

Common: somnolence, headache

Uncommon: dizziness, syncope

Cardiac disorders

Uncommon: congestive heart failure, palpitations

Vascular disorders

Common: hypertension

Respiratory, thoracic and mediastinal disorders

Uncommon: rhinitis, nasal dryness

Gastrointestinal disorders

Common: oral dryness

Uncommon: taste perversion, nausea, diarrhoea

Skin and subcutaneous tissue disorders

Common: eyelid oedema, eyelid pruritus, eyelid erythema

Uncommon: allergic contact dermatitis

General disorders and administration site conditions

Common: asthenic conditions

The following adverse drug reactions have been reported since Brimonidine Tartrate and Timolol Maleate Eye Drops has been marketed:

Eye disorders

Not known: vision blurred

Cardiac disorders

Not known: arrhythmia, bradycardia, tachycardia

Vascular disorders

Not known: hypotension

Skin disorders
Not known: erythema facial
Additional adverse events that have been seen with one of the components and may
potentially occur also with Brimonidine Tartrate and Timolol Maleate Eye Drops:
Brimonidine Eye disorders: iritis, iridocyclitis (anterior uveitis), miosis
Psychiatric disorders: insomnia Respiratory, thoracic and mediastinal disorders: upper respiratory symptoms, dyspnoea Gastrointestinal disorders: gastrointestinal symptoms
General disorders and administration site conditions: systemic allergic reactions
Skin and subcutaneous tissue disorders: - skin reaction including erythema, face oedema, pruritus, rash and vasodilatation
In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants (less than 2 years of age) receivingbrimonidine.
A high incidence and severity of somnolence has been reported in children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ⩽ 20 Kg.
Timolol
Like other topically applied ophthalmic drugs, Brimonidine Tartrate and Timolol Maleate Eye Drops are absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents.
Incidence of systemic adverse drug reactions after topical ophthalmic administration is lower than for systemic administration.
Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with Brimonidine Tartrate and Timolol Maleate Eye Drops are listed below:
Immune system disorders: systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritis, anaphylactic reaction
Metabolism: hypogycaemia
Psychiatric disorders: insomnia, nightmares, memory loss
Nervous system disorders: cerebrovascular accident, cerebral ischemia, increases in signed and symptoms of myasthenia gravis, paraesthesia
Eye disorders: keratitis, choroidal detachment following filtration sugery, decreased corneal sensitivity, corneal erosion, ptosis, diplopia
Cardiac disorders: chest pain, oedema, atrioventricular block, cardiac arrest, cardiac failure
Vascular disorders: Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic, and mediastinal disorders: bronchospasm (predominantly in patients with pre-existing bronchospatic disease), dyspnoea, cough.
Gastrointestinal disorders: dyspepsia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders: alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Musculoskeletal and connective tissue disorders: myalgia
Reproductive system and breast disorders: sexual dysfunction, decreased libido
General disorders and administration site conditions: fatigue
Adverse reactions reported in eye drops containing phosphates:
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Overdosage

Rare reports of overdosage with Brimonidine Tartrate and Timolol Maleate Eye Drops in humans resulted in no adverse outcome. Treatment of an overdose includes supportive and symptomatic therapy; a patient's airway should be maintained.

Brimonidine

Ophthalmic overdose (Adults)

In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion (Adults)

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension. Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness and cardiac arrest. A study of patients showed that timolol did not dialyse 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

5 mL of clear, pale yellow coloured 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 :

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