BRIMOCOM Eye Drops (Brimonidine tartrate 0.2% + Timolol maleate 0.5%)

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

Qualitative and Quantitative Composition

Each ml contains
Brimonidine tartrate.....2 mg
Timolol maleate IP equivalent to timolol.....5 mg
Benzalkonium chloride (as preservative).....0.005% w/v
Isotonic aqueous vehicle.....q.s

Dosage Form and Strength

Ophthalmic solution containing Brimonidine tartrate 2 mg and Timolol maleate 5 mg

Clinical Particulars

Therapeutic Indications

Brimonidine tartrate 2 mg /timolol maleate 5 mg ophthalmic solution is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with chronic open angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta blockers.

Posology and Method of Administration

The recommended dose in adults is one drop of **BRIMOCOM** ophthalmic solution 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 five 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.

Contraindications

Reactive Airway Disease Including Asthma, COPD

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated in patients with reactive airway disease including bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease.

Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated in patients with sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with a pace-maker, overt cardiac failure and cardiogenic shock.

Neonates and Infants (Under the Age of 2 Years)

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated in neonates and infants (less than 2 years of age).

Hypersensitivity Reactions

Local hypersensitivity reactions have occurred following the use of different components of Brimonidine tartrate and Timolol maleate ophthalmic solution. It is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

Other

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated patients receiving monoamine oxidase (MAO) inhibitor therapy and in patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

Special Warnings and Precautions for Use

Potential for Severe Respiratory or Cardiac Reactions

BRIMOCOM ophthalmic solution contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of cardiovascular, pulmonary and other adverse reactions found with 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 have been reported following systemic or ophthalmic administration of timolol maleate. Additionally, ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension.

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, fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution should be discontinued.

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 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.

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.

Obstructive Pulmonary Disease

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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated should, in general, not receive beta-blocking agents, including fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution.

Potentiation Of Vascular Insufficiency

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution may potentiate syndromes associated with vascular insufficiency. Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution should be used with caution in patients with depression, cerebral or coronary insufficiency, severe peripheral circulatory disturbance/disorders (severe form of Raynaud's disease or Raynaud's syndrome), orthostatic hypotension, or thromboangiitis obliterans.

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.

Some patients have experienced ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution 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/Timolol maleate ophthalmic solution 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 IOP.

Potentiation 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 Hypoglycaemic Symptoms In Patients With Diabetes Mellitus

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

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.

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

Ocular Hypersensitivity

Ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solutions 0.2%, with some reported to be associated with an increase in IOP.

Contamination Of Topical Ophthalmic Products After Use

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.

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 anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. 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.

Pediatric Population

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤20 Kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence. The safety and effectiveness of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution in children and adolescents (2 to 17 years of age) have not been established.

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 IOP 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**.**

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 allergens 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 maleate.

The preservative in **BRIMOCOM** ophthalmic solution, 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.

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution has not been studied in patients with closed-angle glaucoma.

Drug Interactions

Antihypertensives/ Cardiac Glycosides

Because fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution may reduce blood pressure, caution in using drugs such as anti-hypertensives and/or cardiac glycosides with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is advised.

Beta-adrenergic Blocking Agents

Patients who are receiving a beta-adrenergic blocking agent orally and fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution 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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, 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.

CNS Depressants

Although specific drug interaction studies have not been conducted with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

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, fluoxetine, paroxetine, SSRIs) and timolol.

Tricyclic Anti-depressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution in humans can lead to resulting interference with the IOP lowering effect. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine oxidase inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

Patients who have been receiving MAO inhibitor therapy should wait 14 days after discontinuation before commencing treatment with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution.

Others

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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution with systemic anti-hypertensives.

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.

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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution.

Caution must be exercised if fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is used concomitantly with iodine contrast products or intravenously administered lidocain.

Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol.

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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

Use in Special Population

Pregnant Women

Teratogenicity studies have been performed in animals. Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent materno-toxicity.

There are no adequate and well-controlled studies in pregnant women, however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactating Women

Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution 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.

Pediatric Patients

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is contraindicated in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of 2 years.

The safety and effectiveness of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution have been established in the age groups 2-16 years of age. Use of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution in this age group is supported by evidence from adequate and well-controlled studies of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

Geriatric Patients

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

Effects on ability to drive and use machines

Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution has minor influence on the ability to drive and use machines. Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution 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.

Undesirable Effects

Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Fixed Combination of Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution

In clinical trials of 12-months duration with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, allergic contact dermatitis, superficial punctate keratitis, and visual disturbance.

Other adverse reactions that have been reported with the individual components are listed below.

Brimonidine Tartrate (0.1%-0.2%)

Abnormal taste, allergic reaction, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival blanching, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), hordeolum, insomnia, keratitis, lid crusting, lid disorder, muscular pain, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, superficial punctate keratopathy, tearing, upper respiratory symptoms, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

Timolol (Ocular Administration)

Body as a whole: chest pain; *Cardiovascular*: Arrhythmia, bradycardia, cardiac arrest, cardiac failure, tachycardia, cerebral ischemia, congestive heart failure, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, chest pain, Raynaud's phenomenon, syncope, and worsening of angina pectoris; *Digestive*: Anorexia, diarrhea, nausea; *Immunologic*: Systemic lupus erythematosus; *Nervous System/Psychiatric*: Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, 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 generalized and localized rash; *Respiratory*: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, nasal congestion, cough, respiratory failure; *Endocrine*: Masked symptoms of hypoglycemia in diabetes; *Special Senses*: diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus; *Urogenital*: Decreased libido, sexual dysfunction, impotence, Peyronie's disease, retroperitoneal fibrosis.

Post-marketing Experience

The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions, timolol ophthalmic solutions or both in combination, in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, timolol ophthalmic solution, or a combination of these factors, include: bradycardia, depression, eyelid erythema extending to the cheek or forehead, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. In infants, apnea, bradycardia, cyanosis, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression and somnolence have been reported.

Oral Timolol/ Oral Beta-blockers

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: Decreased exercise tolerance, extremity pain, weight loss; Cardiovascular: Vasodilatation, worsening of arterial insufficiency; Digestive: Gastrointestinal pain, abdominal pain, hepatomegaly, ischemic colitis, mesenteric arterial thrombosis, vomiting; Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; Endocrine: Hyperglycemia, hypoglycemia; Skin: Increased pigmentation, pruritus, skin irritation, sweating; Musculoskeletal: Arthralgia, myalgia; Nervous System/Psychiatric: An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometrics, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly clouded sensorium, vertigo, fatigue; Respiratory: Bronchial obstruction, rales; Urogenital: Urination difficulties.

The following adverse drug reactions were reported during clinical trials with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution:

Eye disorders

Very Common (>1/10): conjunctival hyperaemia, burning sensation

Common (>1/100, <1/10): stinging sensation in the eye, allergic conjunctivitis, corneal erosion, superficial punctuate keratitis, eye pruritus, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation

Uncommon (>1/1000, <1/100): visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment

Psychiatric disorders

Common (>1/100, <1/10): depression

Nervous system disorders

Common (>1/100, <1/10): somnolence, headache

Uncommon (>1/1000, <1/100): dizziness, syncope

Cardiac disorders

Uncommon (>1/1000, <1/100): congestive heart failure, palpitations

Vascular disorders

Common (>1/100, <1/10): hypertension *Respiratory, thoracic and mediastinal disorders*

Uncommon (>1/1000, <1/100): rhinitis, nasal dryness

Gastrointestinal disorders

Common (>1/100, <1/10): oral dryness

Uncommon (>1/1000, <1/100): taste perversion, nausea, diarrhoea

Skin and subcutaneous tissue disorders

Common (>1/100, <1/10): eyelid oedema, eyelid pruritus, eyelid erythema

Uncommon (>1/1000, <1/100): allergic contact dermatitis

General disorders and administration site conditions

Common (>1/100, <1/10): asthenic conditions

The following adverse drug reactions have been reported since fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution 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 fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution-

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) receiving brimonidine.

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, fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution is absorbed into the systemic circulation. Absorption of timolol 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.

Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with fixed combination of Brimonidine tartrate and Timolol maleate are listed below:

Immune system disorders: systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritis, anaphylactic reaction

Metabolism: hypoglycaemia

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 surgery, 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.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. Very limited information exists on accidental ingestion of brimonidine in adults alone or in combination. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine ophthalmic solution as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patient's airway should be maintained.

Brimonidine tartrate

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 tartrate 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.

Pediatric Population

Reports of serious adverse effects following inadvertent ingestion of Brimonidine tartrate 0.2% ophthalmic solution by paediatric subjects have been reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6-24 hours.

Timolol

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

Pharmacological Properties

Mechanism of action

BRIMOCOM ophthalmic solution comprised of two components: brimonidine tartrate and timolol maleate, a relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor. Each of these two components decreases elevated IOP, whether or not associated with glaucoma. 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.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. 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.

Pharmacodynamic Properties

Both brimonidine and timolol have a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing for brimonidine and one to two hours for timolol.

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 microvessels associated with human retinal xenografts.

Timolol maleate is a $beta_1$ and $beta_2$ non-selective adrenergic receptor inhibitor that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilizing) activity.

Clinical Studies

Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution administered twice a day (BID) to individually-administered brimonidine tartrate ophthalmic solution, 0.2% administered three times per day (TID) and timolol maleate ophthalmic solution, 0.5% BID in patients with glaucoma or ocular hypertension. Brimonidine tartrate/Timolol maleate ophthalmic solution BID provided an additional 1 to 3 mm Hg decrease in IOP over brimonidine treatment TID and an additional 1 to 2 mm Hg decrease over timolol treatment BID during the first 7 hours post dosing. However, the IOP-lowering of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution BID was less (approximately 1-2 mm Hg) than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine tartrate TID. Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution administered BID had a favorable safety profile versus concurrently administered brimonidine TID and timolol BID in the self-reported level of severity of sleepiness for patients over age 40.

In three controlled, double-masked clinical studies, fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution (twice daily) produced a clinically meaningful additive decrease in mean diurnal IOP compared with timolol (twice daily) and brimonidine (twice daily or three times a day) when administered as monotherapy.

In a study in patients whose IOP was insufficiently controlled following a minimal 3-week run-in on any monotherapy, additional decreases in mean diurnal IOP of 4.5, 3.3 and 3.5 mmHg were observed during 3 months of treatment for fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution (twice daily), timolol (twice daily) and brimonidine (twice daily), respectively. In this study, at trough, a significant additional decrease in IOP could only be demonstrated on comparison with brimonidine but not with timolol, however a positive trend was seen with superiority at all other timepoints. In the pooled data of the other two trials statistical superiority versus timolol was seen throughout.

In addition, the IOP-lowering effect of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution was consistently non-inferior to that achieved by adjunctive therapy of brimonidine and timolol (all twice daily).

The IOP-lowering effect of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution has been shown to be maintained in double-masked studies of up to 12 months.

Pharmacokinetic Properties

Absorption

Systemic absorption of brimonidine tartrate and timolol maleate was assessed in healthy volunteers and patients following topical dosing with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution. Normal volunteers dosed with one drop of Brimonidine tartrate/Timolol maleate ophthalmic solution twice daily in both eyes for seven days showed peak plasma brimonidine tartrate and timolol maleate concentrations of 30 pg/mL and 400 pg/mL, respectively. Plasma concentrations of brimonidine peaked at 1 to 4 hours after ocular dosing. Peak plasma concentrations of timolol occurred approximately 1 to 3 hours post-dose.

In a crossover study of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, brimonidine tartrate 0.2%, and timolol maleate 0.5% administered twice daily for 7 days in healthy volunteers, the mean brimonidine tartrate area-under-the-plasma-concentration-time curve (AUC) for fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution was 128 ± 61 pg·hr/mL versus 141 ± 106 pg·hr/mL for the respective monotherapy treatments; mean C_{max} values of brimonidine tartrate were comparable following Fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution treatment versus monotherapy (32.7 ± 15.0 pg/mL versus 34.7 ± 22.6 pg/mL, respectively). Mean timolol AUC for fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution was similar to that of the respective monotherapy treatment (2919 ± 1679 pg·hr/mL versus 2909 ± 1231 pg·hr/mL, respectively); mean C_{max} of timolol maleate was approximately 20% lower following fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution treatment versus monotherapy.

In a parallel study in patients dosed twice daily with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, twice daily with timolol maleate 0.5%, or three times daily with brimonidine tartrate 0.2%, one-hour post dose plasma concentrations of timolol maleate and brimonidine tartrate were approximately 30-40% lower with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution than their respective monotherapy values. The lower plasma brimonidine tartrate concentrations with fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution appears to be due to twice-daily dosing for Brimonidine tartrate/Timolol maleate ophthalmic solution versus three-times dosing with brimonidine tartrate 0.2%.

Distribution

The protein binding of timolol maleate is approximately 60% and human plasma protein binding of brimonidine tartrate is approximately 29%. Brimonidine binds extensively and reversibly to melanin in ocular tissues without any untoward effects. Accumulation does not occur in the absence of melanin.

Metabolism

Brimonidine tartrate is not metabolised to a great extent in human eyes. In humans, brimonidine tartrate is extensively metabolized by the liver. Timolol maleate is partially metabolized by the liver.

Excretion

In the crossover study in healthy volunteers, the plasma concentration of brimonidine tartrate declined with a systemic half-life of approximately 3 hours. The apparent systemic half-life of timolol maleate was about 7 hours after ocular administration.

Urinary excretion is the major route of elimination of brimonidine tartrate and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine tartrate was eliminated within 120 hours, with 74% found in the urine. Unchanged timolol maleate and its metabolites are excreted by the kidney.

Nonclinical Properties

Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

With brimonidine tartrate, no compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 210 times, respectively, the plasma C drug concentration in humans treated with one drop of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution into both eyes twice daily, the recommended daily human dose. In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day [approximately 25,000 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)]. Similar differences were not observed in rats administered oral doses equivalent to approximately 8,300 times the daily dose of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution in humans.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 42,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 420 to 4,200 times higher, respectively, than the MRHOD). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation

assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats with timolol maleate and in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution.

Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. Non-clinical data reveal no special hazard for humans based on conventional studies of the individual components in safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenicity studies. Additional ocular repeated dose toxicity studies on fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution also showed no special hazard for humans.

Brimonidine

Brimonidine tartrate did not cause any teratogenic effects in animals, but caused abortion in rabbits and postnatal growth reduction in rats at systemic exposures approximately 37-times and 134-times those obtained during therapy in humans, respectively.

Timolol

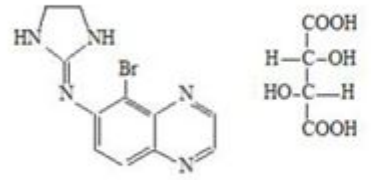
In animal studies, beta-blockers have been shown to produce reduced umbilical blood flow, reduced foetal growth, delayed ossification and increased foetal and postnatal death, but no teratogenicity. With timolol, embryotoxicity (resorption) in rabbit and foetotoxicity (delayed ossification) in rats have been seen at high maternal doses. Teratogenicity studies in mice, rats and rabbits, at oral doses of timolol up to 4200 times of that in the human daily dose of fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution, showed no evidence of foetal malformation.

Description

BRIMOCOM (brimonidine tartrate 2 mg/timolol maleate 5 mg) ophthalmic solution is a fixed combination of relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor (topical IOP lowering agent).

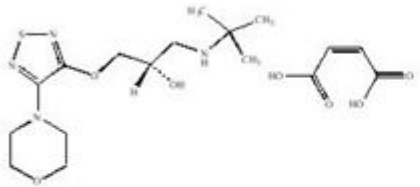
The structural formulae are:

Brimonidine tartrate:



5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate; MW= 442.24

Timolol maleate:



(-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1) (salt); MW= 432.50 as the maleate salt

Pharmaceutical Particulars

Incompatibilities

Not applicable

Shelf- Life

As on the pack.

Packaging Information

BRIMOCOM Eye Drops: Vial of 5 ml

Storage and Handling Instructions

Store in a cool place.

Patient Counselling Information

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

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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 Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

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 multidose 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 **BRIMOCOM** 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 15 minutes following administration of **BRIMOCOM** ophthalmic solution

As with other similar medications, fixed combination of Brimonidine tartrate and Timolol maleate ophthalmic solution may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Details of Manufacturer

Manufactured by CIPLA Ltd**.**

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Ganpatrao Kadam Marg

Lower Parel

Mumbai – 400 013, India

Date of Revision

26/03/2020