Brimopress™-T

1. Generic Names

Brimonidine Tartrate

Timolol Maleate

2. Composition

Brimonidine Tartrate	0.2%
Timolol Maleate	0.5%

3. Dosage form and strength

Topical ophthalmic solution containing Brimonidine Tartrate 0.2% (1mg/100ml) and Timolol Maleate 0.5% (0.5mg/100ml)..

4. Clinical particulars

4.1 Therapeutic indication

BRIMOPRESS-T is indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

- 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)

4.4 Special warnings and precautions for use

- Potentiation of Respiratory Reactions Including Asthma

BRIMOPRESS-T contains timolol maleate; and although administered topically can be absorbed systemically; hence the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate

- Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by betaadrenergic 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, BRIMOPRESS-T should be discontinued.

- 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 BRIMOPRESS-T is contraindicated should, in general, not receive beta-blocking agents.

- Potentiation of Vascular Insufficiency

BRIMOPRESS-T may potentiate syndromes associated with vascular insufficiency. BRIMOPRESS-T should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, 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.

- 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 Hypoglycemic 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. Betaadrenergic 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 betaadrenergic blocking agents that might precipitate a thyroid storm.

- 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 intraocular pressure

- Impairment of Beta-adrenergically Mediated Reflexes During Surgery

Beta-adrenergic receptor blockade impairs the ability of the heart to respond to betaadrenergically 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 betaadrenergic receptor blocking agents.

4.5 Drug interactions

- Antihypertensives/cardiac glycosides may lower blood pressure.
- Concomitant use with systemic beta-blockers may potentiate systemic betablockade.
- Oral or intravenous calcium antagonists may cause atrioventricular conduction disturbances, left ventricular failure, and hypotension.
- Catecholamine-depleting drugs may have additive effects and produce hypotension and/or marked bradycardia.
- Use with CNS depressants may result in an additive or potentiating effect.
- Digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.
- CYP2D6 inhibitors may potentiate systemic beta-blockade.
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine.
- Monoamine oxidase inhibitors may result in increased hypotension.

4.6 Use in special population

- Pediatric: The safety and effectiveness of BRIMOPRESS-T have not been studied in pediatric patients below the age of 2 years. BRIMOPRESS-T is not recommended for use in pediatric patients under the age of 2 years
- Geriatric: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.
- Liver impairment: BRIMOPRESS T has not been studied in patients with hepatic impairment.
- Renal failure: BRIMOPRESS T has not been studied in patients with renal impairment. The effect of dialysis on Brimonidine pharmacokinetics in patients with renal failure is not known
- Pregnancy and lactation: Pregnancy Category C: Teratogenicity studies have been performed in animals. There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fatal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, BRIMOPRESS-T should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

  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 BRIMOPRESS-T in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to BRIMOPRESS-T is known.

4.8 Undesirable effects

Adverse events occurring in approximately 10-30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus. Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain. The following adverse reactions

were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

4.9 Overdose

There have been reports of inadvertent over dosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic betaadrenergic 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 solutions as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

5. Pharmacological properties

5.1 Mechanism of action

Brimonidine is a relatively selective alpha-2 adrenergic receptor agonist with a peak ocular hypotensive effect occurring at two hours post-dosing. Fluor photometric studies in animals and humans suggest that Brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing Uveosceleral outflow.

The precise mechanism of the ocular hypotensive action of TIMOLOL is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduce aqueous formation. However, in some studies a slight increase in outflow facility was also observed. TIMOLOL ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma.

5.2 Pharmacodynamic properties

Brimonidine Tartrate has a peak ocular hypotensive effect occurring at two hours post-dosing. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters

Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this

blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time 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.

5.3 Pharmacokinetic properties

After ocular administration of a 0.1% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. The protein binding of Brimonidine has not been studied. In humans brimonidine is extensively metabolized by the liver. Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the urine

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged Timolol. Timolol is not removed by haemodialysis.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

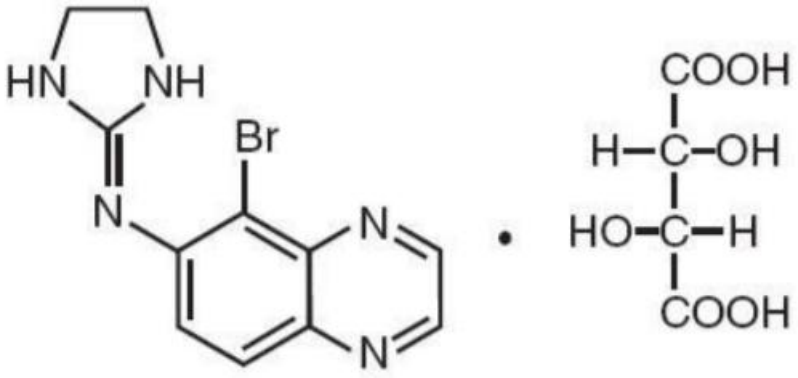
6-month ocular/systemic study in rabbits and the 1-year ocular/systemic study in monkeys with 0.2, 0.5, and 0.8% brimonidine ophthalmic formulations showed no ocular or organ toxicity. The highest concentration of 0.8% used in rabbits and monkeys resulted in plasma drug concentrations of 95 (Cmax) and 10 (C2hr) times, respectively, higher than those seen in humans following topical dosing. Dose-related transient exaggerated pharmacologic

effects of sedation were observed in the 1-year oral study in monkeys without any organ toxicity. The dose that elicited an apparent pharmacologic effect produced a plasma drug concentration that was approximately 115 times higher than that in humans. In 2-year carcinogenicity studies in mice and rats using doses that produced plasma concentrations 77 and 118 times, respectively, higher than those seen in humans, no oncogenic effect was observed.

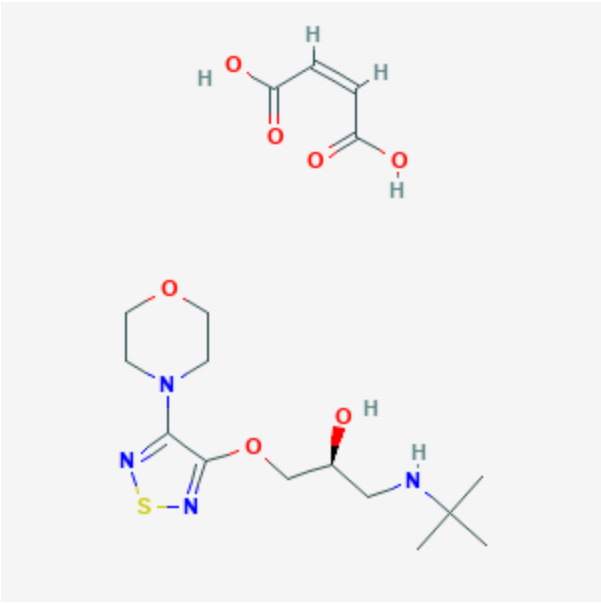
No adverse ocular effects were observed in rabbits and dogs administered with timolol maleate topically in studies lasting one and two years, respectively. The oral LD50 of the medicine is 1190 and 900mg/kg in female mice and female rats, respectively.

7. Description

Brimonidine is a relatively selective alpha-2 adrenergic receptor agonist (topical intraocular pressure lowering agent). The structural formula of brimonidine tartrate is: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate; MW= 442.24.



Timolol Maleate is the maleate salt form of timolol, a propanolamine derivative and a non-selective beta-adrenergic antagonist with antihypertensive property. Chemical name is (*Z*)-but-2-enedioic acid;(2*S*)-1-(*tert*-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol. Molecular weight is 432.5 g/mol. The structure formula is:



The empirical formula is $C_{17}H_{28}N_4O_7S$. Timolol maleate is a white odourless, crystalline powder which is soluble in water, methanol and alcohol and has a melting point of 201.5° C to 202.5° C.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

36 months.

8.3 Packaging Information

BRIMOPRESS-T is supplied sterile in 5 ml lupolen transparent plastic bottles.

8.4 Storage and handling instructions

Store in a cool, dry and dark place only

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by CENTAUR PHARMACEUTICALS PVT. LTD. and DCI Pharmaceuticals

11. Details of permission or license number with date

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