BRIMOPRESS-T EYE DROPS

COMPOSITION

Each ml of BRIMOPRESS-T EYE DROPS contains

Brimonidine Tartarate	0.2%
Timolol Maleate	0.5%

BRIMOPRESS-T ophthalmic solution is a combination of Brimonidine Tartrate, relatively selective alpha-2 adrenergic agonist & Timolol Maleate, a beta adrenergic receptor inhibitor, for ophthalmic use.

CLINICAL PHARMACOLOGY

Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Higher the level of intraocular pressure, greater the risk of glaucomatous field loss and optic nerve damage.

BRIMOPRESS-T contains relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor. 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. It is thought that brimonidine tartrate lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation.

Timolol is a $beta_1$ and $beta_2$ 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.

BRIMOPRESS-T decreases elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone

INDICATIONS AND USAGE

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

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)

PRECAUTIONS

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 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, **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. 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 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.

DRUG INTERACTIONS:

- Antihypertensives/cardiac glycosides may lower blood pressure.
- Concomitant use with systemic beta-blockers may potentiate systemic beta-blockade.
- 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Brimonidine Tartrate was not mutagenic or cytogenic in a series of in vitro and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

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 Similar differences were not observed in rats administered oral doses equivalent to approximately 8,300 times the daily dose of **Timolol + Brimonidine** in humans. 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).

Pregnancy: Teratogenic Effects:

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 fetal 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 fetus.

Nursing Mothers:

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.

Pediatric Use:

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 Use:

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

ADVERSE REACTIONS

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.

OVERDOSAGE

There have been reports of inadvertent over dosage 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 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.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **BRIMOPRESS-T** 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.

PRESENTATION

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

NOTE: Store in a cool, dry and dark place only.