EyeKare

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

BrimoEye®-T

Brimonidine Tartrate & Timolol Maleate Ophthalmic Solution

COMPOSITION

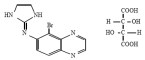
Brimonidine Tartrate IP 0.2% w/v, Timolol Maleate IP equivalent to Timolol 0.5% w/v, Water for Injections IP q.s.

DESCRIPTION

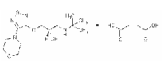
BRIMOEYE-T (Brimonidine Tartrate & Timolol Maleate Ophthalmic Solution) 0.2% w/v & 0.5% w/v respectively, sterile, is a relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor (topical intraocular pressure lowering agent).

The structural formulae are:

Brimonidine Tartrate:



Timolol Maleate:



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

(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (salt); MW=432.50 as the maleate salt In solution, BRIMOEYE-T (Brimonidine Tartrate & Timolol Maleate ophthalmic solution) 0.2% w/v & 0.5% w/v respectively has a clear, greenish-yellow color. It has an osmolality of 260-330 mOsmol/kg and a pH during its shelf life of 6.5-7.3.

Brimonidine Tartrate appears as an off-white, or white to pale-yellow powder and is soluble in both water (1.5 mg/ml) and in the product vehicle (3 mg/ml) at pH 7.2. Timolol Maleate appears as a white, odorless, crystalline powder and is soluble in water, methanol, and alcohol.

BRIMOEYE-T contains the active ingredients Brimonidine Tartrate 0.2% w/v and Timolol Maleate 0.5% w/v in Water for Injections IP q.s.

CLINICAL PHARMACOLOGY

• Mechanism of Action

BRIMOEYE-T is comprised of two components: Brimonidine Tartrate & Timolol Maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

BRIMOEYE-T is a 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.

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 Maleate is a beta and beta$_2$adrenergic receptor inhibitor that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity**.**

• Pharmacokinetics

Absorption

Systemic absorption of Brimonidine and Timolol was assessed in healthy volunteers and patients following topical dosing with BRIMOEYE-T**.** Normal volunteers dosed with one drop of BRIMOEYE-T twice daily in both eyes for seven days showed peak plasma Brimonidine and Timolol 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 BRIMOEYE-T, Brimonidine Tartrate 0.2% w/v & Timolol Maleate 0.5% w/v administered twice daily for 7 days in healthy volunteers, the mean Brimonidine area-under-the-plasma-concentration-time curve (AUC) for BRIMOEYE-T was 128 ± 61 pg•hr/ml versus 141 ± 106 pg•hr/mL for the respective monotherapy treatments; mean Cmax values of Brimonidine were comparable following BRIMOEYE-T treatment versus monotherapy (32.7 ± 15 pg/ml versus 34.7 ± 22.6 pg/ml, respectively). Mean Timolol AUC for BRIMOEYE-T was similar to that of the respective monotherapy treatment (2919 ± 1679 pg•hr/ml versus 2909 ± 1231 pg•hr/ml, respectively); mean Cmax of Timolol was approximately 20% lower following BRIMOEYE-T treatment versus monotherapy**.**

In a parallel study in patients dosed twice daily with BRIMOEYE-T, twice daily with Timolol 0.5% w/v, or three times daily with Brimonidine Tartrate 0.2% w/v, one-hour post dose plasma concentrations of Timolol and Brimonidine were approximately 30-40% lower with BRIMOEYE-T than their respective monotherapy values.

The lower plasma Brimonidine concentrations with BRIMOEYE-T appears to be due to twice-daily dosing for BRIMOEYE-T versus three-times dosing with Brimonidine Tartrate 0.2% w/v**.**

• Distribution

The protein binding of Timolol is approximately 60%. The protein binding of Brimonidine has not been studied.

• Metabolism

In humans, Brimonidine is extensively metabolized by the liver**.** Timolol is partially metabolized by the liver**.**

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

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. Unchanged Timolol and its metabolites are excreted by the kidney**.**

NONCLINICAL TOXICOLOGY

• 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. The plasma Cmax drug concentration in humans treated with one drop of BRIMOEYE-T 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).

CLINICAL STUDIES

Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of BRIMOEYE-T administered twice a day (BID) to individually-administered Brimonidine Tartrate ophthalmic solution, 0.2% w/v administered three times per day (TID) and Timolol Maleate ophthalmic solution, 0.5% w/v BID in patients with glaucoma or ocular hypertension. BRIMOEYE-T 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 BRIMOEYE-T BID was less (approximately 1-2 mm Hg) than that seen with the concomitant administration of 0.5% w/v Timolol BID and 0.2% w/v Brimonidine Tartrate TID. BRIMOEYE-T 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.

INDICATIONS AND USAGE

BRIMOEYE-T (Brimonidine Tartrate & Timolol Maleate Ophthalmic Solution) 0.2% w/v & 0.5% w/v respectively is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor 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; the IOP-lowering of BRIMOEYE-T dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% w/v Timolol Maleate ophthalmic solution dosed twice a day and 0.2% w/v Brimonidine Tartrate ophthalmic solution dosed three times per day.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of BRIMOEYE-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.

DOSAGE FORMS AND STRENGTHS

Solution containing 2 mg/ml Brimonidine Tartrate and 5 mg/ml Timolol (6.8 mg/ml Timolol Maleate).

CONTRAINDICATIONS

- **Asthma, COPD**

BRIMOEYE-T is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease.

- **Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock**

BRIMOEYE-T is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure cardiogenic shock.

- **Neonates and Infants** (Under the Age of 2 Years)

BRIMOEYE-T is contraindicated in neonates and infants (under the age of 2 years).

- **Hypersensitivity Reactions**

Local hypersensitivity reactions have occurred following the use of different components of BRIMOEYE-T.
BRIMOEYE-T is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

- **Potentiation of Respiratory Reactions Including Asthma**

BRIMOEYE-T contains Timolol Maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Ocular hypersensitivity reactions have been reported with Brimonidine Tartrate ophthalmic solutions 0.2% w/v, with some reported to be associated with an increase in intraocular pressure.

- **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 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. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

ADVERSE REACTIONS

- **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.
BRIMOEYE-T, 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, 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 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 disorder, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, taste perversion, tearing, 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, cerebral ischemia, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, 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, respiratory failure; Endocrine: Masked symptoms of hypoglycemia in diabetes patients
Special Senses: Diplopia, choroidal detachment following filtration surgery,cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus;
Urogenital: Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

DRUG INTERACTIONS

- **Antihypertensives/Cardiac Glycosides**

Because BRIMOEYE-T may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with BRIMOEYE-T is advised.

- **Beta-adrenergic Blocking Agents**

Patients who are receiving a beta-adrenergic blocking agent orally and BRIMOEYE-T 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 BRIMOEYE-T, 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 BRIMOEYE-T, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) 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, SSRIs) and Timolol.

- 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 BRIMOEYE-T 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 and potentially result in an increased systemic side effect such as hypotension. Caution, however, is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

Pregnancy

Pregnancy Category C: 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 BRIMOEYE-T, 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 maternotoxicity**.**
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, BRIMOEYE-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 BRIMOEYE-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**

BRIMOEYE-T is contraindicated in children under the age of 2 years. Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving Brimonidine. The safety and effectiveness of Brimonidine Tartrate & Timolol Maleate have not been studied in children below the age of 2 years.
The safety and effectiveness of BRIMOEYE-T have been established in the age groups 2 – 16 years of age. Use of BRIMOEYE-T in these age groups is supported by evidence from adequate and well-controlled studies of BRIMOEYE-T in adults with additional data from a study of the concomitant use of Brimonidine Tartrate ophthalmic solution 0.2% w/v and Timolol Maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, Brimonidine Tartrate ophthalmic solution 0.2% w/v was dosed three times a day as adjunctive therapy to beta-blockers.

- **Geriatric Use**

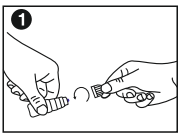
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

PACKAGING :
BRIMOEYE-T is supplied in 5ml and 10ml plastic dropper vials which are specially designed to avoid contamination due to non sterile air or other causes.

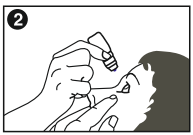
Storage: Store at a temperature not exceeding 30°C and protect from light.

PATIENT 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.
Always replace the cap after using. If solution changes color or becomes cloudy, do not use.
Do not use the product after the expiry date marked on the vial.
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.
Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of BRIMOEYE-T.
As with other similar medications, BRIMOEYE-T 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.

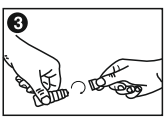
INSTRUCTIONS FOR USE



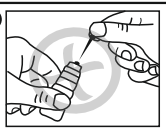
- Turn the cap anti-clockwise to open the vial.



- Turn the vial upside down.
- Look at the blue tip of the vial & align it in center of the eye.
- Squeeze the vial to deliver the drop.



- Tighten it firmly & keep the vial closed for further use.



- **Do not pierce / puncture the vial to open.**

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