

BAUSCH + LOMB

Rimoflo™ T (Brimonidine + Timolol Eye Drops)

GENERIC NAME

(Brimonidine + Timolol) 0.2% w/v/0.5% w/v

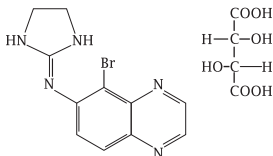
DOSAGE FORM

Ophthalmic Solution

DESCRIPTION

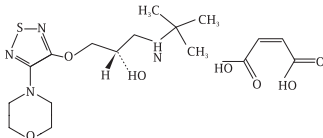
Brimonidine + Timolol Eye Drops, sterile, is a relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor (topical intraocular pressure lowering agent). The structural formulae are:

Brimonidine tartrate:



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 In solution, Brimonidine + Timolol Eye Drops 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 (3.0 mg/mL) at pH 7.2. Timolol maleate appears as a white, odorless, crystalline powder and is soluble in water, methanol, and alcohol or sodium hydroxide to adjust pH.

COMPOSITION

Active: Brimonidine Tartrate 0.2% w/v

Timolol Maleate IP equivalent to Timolol 0.5% w/v

Inactive Ingredients: Sodium chloride, Disodium EDTA, Sodium dihydrogen Phosphate dihydrate, Disodium hydrogen phosphate, Sodium hydroxide, Water for Injections

Preservative Added: Benzalkonium Chloride Solution 0.02% v/v

INDICATIONS

Rimoflo™ T indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who are insufficiently responsive to topical Beta Blockers.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of Rimoflo™ 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.

USE IN SPECIAL POPULATIONS

Pregnancy

Category C: Teratogenicity studies in animals have shown that Brimonidine tartrate is 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 (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with Brimonidine + Timolol Eye Drops, 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)] have been shown to demonstrate no evidence of foetal malformations. Although delayed foetal ossification is reported 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) are reported to be maternotoxic in mice and resulted in an increased number of foetal resorptions. Increased foetal resorptions were also reported 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 foetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, Brimonidine + Timolol Eye Drops should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Nursing Mothers

Timolol has been reported 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 Brimonidine + Timolol Eye Drops 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

Brimonidine + Timolol Eye Drops is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypotension, hypothermia, hypotonia, 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 Brimonidine + Timolol Eye Drops have been established in the age group 2 – 16 years of age. Use of Brimonidine + Timolol Eye Drops in this





age group is supported by evidence from adequate and well-controlled studies of Brimonidine + Timolol Eye Drops 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 of 7 years of age or older (>20 kg), somnolence has been reported to occur less frequently (25%). In the reported study, approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued due to somnolence.

Geriatric Use

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

Hepatic Impairment

Brimonidine + Timolol Eye Drops has not been studied in patients with hepatic impairment.

Renal Impairment

Brimonidine + Timolol Eye Drops has not been studied in patients with renal impairment.

A study of patients with renal failure reported that timolol was not readily removed by dialysis. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

Following oral administration of timolol maleate, the plasma half-life of timolol is essentially unchanged in patients with moderate renal insufficiency.

CONTRAINDICATIONS

Asthma, COPD

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

Hypersensitivity Reactions

Rimoflo™ T is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

WARNINGS AND PRECAUTIONS

FOR EXTERNAL USE ONLY. NOT FOR INJECTION

Potential of Respiratory Reactions Including Asthma

Brimonidine + Timolol Eye Drops 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. 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.

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, Brimonidine + Timolol Eye Drops should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (COPD) 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 Brimonidine + Timolol Eye Drops is contraindicated should, in general, not receive beta-blocking agents, including Brimonidine + Timolol Eye Drops.

Potential of Vascular Insufficiency

Brimonidine + Timolol Eye Drops may potentiate syndromes associated with vascular insufficiency. Brimonidine + Timolol Eye Drops should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis 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.

Potential 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 beta-adrenergic blocking agents that might precipitate a thyroid storm.

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.

DRUG INTERACTIONS

Antihypertensives/Cardiac Glycosides

Because Brimonidine + Timolol Eye Drops may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with Brimonidine + Timolol Eye Drops is advised.

Beta-adrenergic Blocking Agents

Patients who are receiving a beta-adrenergic blocking agent orally and Brimonidine + Timolol Eye Drops 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 Brimonidine + Timolol Eye Drops, 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 Brimonidine + Timolol Eye Drops, 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

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 Brimonidine + Timolol Eye Drops 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 is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

UNDESIRABLE EFFECTS

Clinical Studies Experience

A clinical trial of 12 months duration with Brimonidine + Timolol Eye Drops, indicates allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging as the most frequent reactions occurring in association with its use, occurring in approximately 5% to 15% of the patients. 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 undesirable 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, behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; Skin: Alopecia, psoriasisiform 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.



Postmarketing Experience Brimonidine

The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions 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, or a combination of these factors, include: bradycardia, depression, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

Oral Timolol/Oral Beta-blockers

The following additional undesirable 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, 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; 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; Respiratory: Bronchial obstruction, rales; Urogenital: Urination difficulties.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics

Mechanism of Action:

Rimolfo™ T is comprised of two components: brimonidine tartrate and timolol. 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. Rimolfo™ T is a 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 nonpressure dependent uveoscleral outflow. Timolol maleate is a β_1 and β_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 has been reported in healthy volunteers and patients following topical dosing with Brimonidine + Timolol Eye Drops. Normal volunteers dosed with one drop of Brimonidine + Timolol Eye Drops twice daily in both eyes for seven days indicate 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 Brimonidine + Timolol Eye Drops, brimonidine tartrate 0.2%, and timolol 0.5% administered twice daily for 7 days in healthy volunteers, the mean brimonidine area-under-the-plasma-concentration-time curve (AUC) for Brimonidine + Timolol Eye Drops was 128 ± 61 pg•hr/ml versus 141 ± 106 pg•hr/mL for the respective monotherapy treatments; mean C_{max} values of brimonidine were comparable following Brimonidine + Timolol Eye Drops treatment versus monotherapy (32.7 ± 15.0 pg/mL versus 34.7 ± 22.6 pg/mL, respectively). Mean timolol AUC for Brimonidine + Timolol Eye Drops 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 was approximately 20% lower following Brimonidine + Timolol Eye Drops treatment versus monotherapy. In a parallel study in patients dosed twice daily with Brimonidine + Timolol Eye Drops, twice daily with timolol 0.5%, or three times daily with brimonidine tartrate 0.2%, one-hour post dose plasma concentrations of timolol and brimonidine were approximately 30-40% lower with Brimonidine + Timolol Eye Drops than their respective monotherapy values. The lower plasma brimonidine concentrations with Brimonidine + Timolol Eye Drops appears to be due to twice-daily dosing for Brimonidine + Timolol Eye Drops versus three-times dosing with brimonidine tartrate 0.2%.

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.

CLINICAL STUDIES

The available clinical studies compare the IOP-lowering effect over the course of the day of Brimonidine + Timolol Eye Drops 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 + Timolol Eye Drops 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 Brimonidine + Timolol Eye Drops BID was less (approximately 1-2 mm Hg) than that reported with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine tartrate TID. Brimonidine + Timolol Eye Drops 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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

With brimonidine tartrate, no compound-related carcinogenic effects were documented 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 Cmax drug concentration in humans treated with one drop of Brimonidine + Timolol Eye Drops 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 Brimonidine + Timolol Eye Drops 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 demonstrate 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 Brimonidine + Timolol Eye Drops

OVERDOSE

No information is available on overdosage with Brimonidine + Timolol Eye Drops in humans. 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. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

INFORMATION FOR PATIENTS

- Rimoflo™ T is sterile when packed. Patient are advised not to allow the dropper tip/ dispensing tip to touch any surface, as this may contaminate the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.
- If solution changes color or becomes cloudy, it is advised that patients must not use it.
- Do not use the product after the expiration date marked on the bottle.
- If patients have ocular surgery or develop an intercurrent ocular condition (e.g. trauma or infection), immediately seek 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 and only after consultation with medical practitioner.
- 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 not take this product.
- Contact lenses should be removed prior to administration of Rimoflo™ T. Lenses may be reinserted 15 minutes following administration of the drug.
- As with other similar medications, Brimonidine + Timolol Eye Drops may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities are cautioned of the potential for a decrease in mental alertness.

INCOMPATIBILITIES

No incompatibility studies are reported.

SHELF LIFE

Please see Mfg. Date/ Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.



PACKAGING INFORMATION

Rimoflo™ T (Brimonidine + Timolol Eye Drops) is supplied in a 5 ml plastic bottle with a white cap.

STORAGE AND HANDLING INSTRUCTIONS

Keep in a cool place. Protect from light.

Use the solution within one month after opening the container.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REFERENCES:

Prescribing Information of Allergan, 04/2011. Information compiled on December 2011

Marketed by:

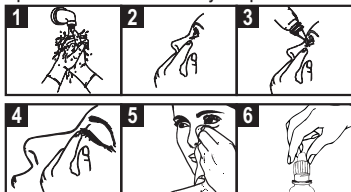
BAUSCH & LOMB EYECARE (I) PVT. LTD.
R-13 & 14, Ansal Chambers-II,
6 Bhikaji Cama Place,
New Delhi 110066

Manufactured in India by:

Micro Labs Limited
Plot No: 113 to 116, 4th Phase;
K.I.A.D.B., Bommasandra Industrial Area,
Bangalore-560099

©/TM are trademarks of Bausch & Lomb or its affiliates
All other product / brand names are trademarks
of their respective owners.

Tips for Safe Administration of Eye Drops*



1. Wash your hands thoroughly before administration.
2. Bend your head backwards and gently pull your lower eyelid down.
3. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.
5. Wipe away any liquid that falls onto your cheek with a tissue.
6. Close the cap immediately after use.

Take Care of your eye drops:

- Do not let the dropper or dispensing tips touch your eye, finger, or any other surface.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If more than one type of Eye Drops are used, wait for at least five minutes before administering the second medication to avoid washout of the previous drug.
- Consult your physician if eye symptoms become worse after using eye drops.

*Read this entire leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you have any further questions, ask your Physician.