BRIMOPRESS® T

BRIMONIDINE TARTRATE 0.2%
TIMOLOL 0.5%

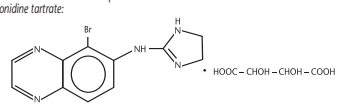
STERILE OPHTHALMIC SOLUTION

Made in Argentina - Rx ONLY

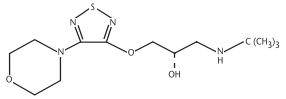
Formula:
Each 100 ml of the ophthalmic solution contains:
Brimonidine tartrate 200 mg
Timolol maleate 680 mg (equivalent to 500 mg of Timolol)
Sodium chloride 320 mg; Benzalkonium chloride 5 mg; Sodium edetate dihydrate 10 mg; Monosodium phosphate dihydrate 210 mg; Anhydrous disodium phosphate 758 mg; Purified water q.s. 100 ml.

The volume of each BRIMOPRESS® T drop is 0.033 ml.
Dose of Brimonidine tartrate per drop: 0.066 mg/drop.
Dose of Timolol per drop: 0.165 mg/drop.

Therapeutic action:
Combination medication for ophthalmic topical use consisting of a beta-adrenergic blocking agent (Timolol) and an alpha$_2$ adrenergic agonist agent (Brimonidine), which reduces the intra-ocular pressure (IOP).
ATC Classification: S01ED51.
Chemical structure of the components:
Brimonidine tartrate:



Timolol:



Indications of use:
Treatment for high intra-ocular pressure (IOP) in patients with ocular hypertension and/or open-angle type glaucoma when a local treatment based on a combination of an alpha$_2$ adrenergic agonist agent and a beta-adrenergic blocking agent is recommended and in patients intolerant to other medications or whose response is insufficient.

Pharmacological characteristics / Properties:
Pharmacological action
BRIMOPRESS® T (0.2% Brimonidine /0.5% Timolol ophthalmic solution) reduces the intra-ocular pressure (IOP) by reducing aqueous humor production and by increasing the uveoscleral outflow. Each BRIMOPRESS® T component is individually used for controlling the IOP.
Brimonidine is an alpha$_2$ adrenergic receptor agonist. Fluorophotometric studies conducted in animals and human beings show that Brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and by increasing uveoscleral outflow. The maximum hypotensive effect is reached after two hours of dose application.
Timolol maleate is a non-selective, beta1 and beta2 adrenergic receptor blocking agent lacking intrinsic sympathomimetic effect and with no significant membrane stabilizing action. Timolol decreases the intra-ocular pressure by reducing aqueous humor production. Lowering of high intra-ocular pressure after Timolol administration is usually detected within the first half hour of a dose application. The maximum effect is generally detected from 1 to 2 hours after application, with significant IOP reductions being kept for 24 hours after a single dose administration.
Pharmacokinetics
Plasma concentrations of 0.2% Brimonidine solution after ocular administration peaks within the first and fourth hour and declines with a mean systemic half-life of about 3 hours.
Systemic Brimonidine metabolism in human beings is extensive. Drug metabolism mainly occurs in the liver. Urinary excretion is the main elimination route of the drug and its metabolites. About 87% of an orally administered radioactive dose was eliminated within 120 hours, with 74% of it being found in urine.
After an oral administration, Timolol is rapidly and completely absorbed (about 90%). Plasma Timolol is detected within half an hour of the administration, and plasma peaks are observed after 2 hours of intake. Plasma half-life is about 4 hours, which remains mostly the same value in patients suffering from moderate renal failure. Timolol is partially metabolized in the liver and excreted through the kidney along with its metabolites. Timolol binding to plasma proteins is not extensive.

Posology and Way of administration:
BRIMOPRESS® T recommended posology is one drop in affected eye(s) twice daily approximately 12 hours apart. When other topical ophthalmic anti-glaucoma drugs are replaced by BRIMOPRESS® T, their use should be discontinued after the administration corresponding to that change day and start BRIMOPRESS® T treatment the following day. If other topical ophthalmic drugs are being used, the administration interval between BRIMOPRESS® T and the other drugs should be at least 10 minutes.

Contraindications:
Absolute contraindications
Known hypersensitivity to any product components.
Contraindications related to beta-adrenergic blocking agents:
Timolol, as many topical ophthalmic drugs, is systemically absorbed. After the topical application, the same adverse reactions observed for systemic application of beta-adrenergic blocking agents may occur:
- Bronchial asthma or history of bronchial asthma.
- Severe chronic obstructive pulmonary diseases.
- Clear cardiac failure.
- Cardiogenic shock.
- Second or third degree atrioventricular block.
- Prinzmetal's angina.
- Sinus bradycardia (< 45 to 50 contractions per minute) or any dysfunction of the sinus node.
- Raynaud's disease and other peripheral circulatory disorders.
- Clear pheochromocytoma.
- Hypotension.
- Drug-drug interaction with floctafenine or sultopride.

Contraindications related to alpha$_2$ adrenergic receptor agonists:
- Patients under treatment with monoamine oxidase inhibitors (MAO).

Warnings:
For topical ophthalmic use exclusively. The preservative of BRIMOPRESS® T -benzalkonium chloride- can be absorbed by soft contact lenses; patients wearing soft contact lenses should wait for at least 15 minutes after each instillation to insert the lenses again.
Intolerance to wearing contact lenses may occur due to a decrease in tear secretion generally related to beta-adrenergic blocking agents.
To avoid content contamination, the dispensing container tip should not be in contact with any surfaces and the cap should be immediately replace after using.
Wear the product only when the container is intact.
The container tip should not be in contact neither with the eye nor with surrounding anatomical structures.
The product should not be used after the expiration date.
Timolol:
Cases of choroid detachment have been reported due to ocular hyponia after surgical treatment for glaucoma with anti-glaucoma agents acting by decreasing aqueous humor secretion (Timolol, acetazolamide).
Timolol is systemically absorbed as many topical ophthalmic drugs. After the topical application, the same adverse reactions observed for systemic application of beta-adrenergic blocking agents may occur:
Cardiac failure: Sympathetic stimulation may be essential for supporting of circulation in individuals with diminished myocardial contractility; the inhibition of beta-adrenergic receptor blockade by beta receptor blocking agents 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 diseases: Patients with chronic obstructive pulmonary disease (for example, chronic bronchitis or emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma , in which BRIMOPRESS® T is contraindicated should, in general, not receive beta-blockers.
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.
Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicity should be managed carefully since abrupt withdrawal of beta-adrenergic blocking agents might precipitate a "thyroid storm".
Pheochromocytoma: Beta-adrenergic blocking agents administered to patients with treated pheochromocytoma require a close monitoring of the arterial pressure.
Renal and/or liver failure: The systemic administration of beta blockers normally requires dosage adaptation in cases of risk.
Psoriasis: Cases of psoriasis exacerbation have been reported, the indication of beta blockers should be carefully evaluated in these patients.
Allergic reactions: Using beta blocking agents in patients suspected of developing severe anaphylactic reactions or under desensitizing treatments may worsen the reaction and develop resistance to treatment with adrenaline.
General anesthesia: Beta blockers cause attenuation of the sympathetic reflex reactions, which may augment the risk of general anesthesia in surgical procedures. Treatment with beta blockers decreases the risk of arrhythmia, myocardial ischemia, and perioperative hypertensive processes. It is advisable to inform the anesthesiologist the patient is under treatment with beta blockers.
Suspension of the treatment: Treatment with beta blockers should not be stopped abruptly, abrupt suspension of treatment may cause severe arrhythmias, myocardial infarct, or sudden death.
Bradycardia: If the heart beat is lower than 50 to 55 beats per minute while at rest and patient shows bradycardia-related symptoms, the posology should be decreased.
First degree atrioventricular block: Due to the positive dromotropic effect of the beta blockers, this type of drugs should be cautiously administered to these patients.

Precautions:
The intra-ocular pressure of patients under treatment with medications to lower their IOP should be frequently monitored.
Timolol:
Due to the effects of the beta-adrenergic blockers on the blood pressure and pulse, these agents should be cautiously used in patients with cerebrovascular failure. If the symptoms and signs indicate a reduction of the brain blood flow after the start of BRIMOPRESS® T therapy, an alternative treatment should be considered.
Cases of bacterial-related keratitis with the use of multi-dose dispensers containing topical ophthalmologic drugs have been observed. In those cases, the multi-dose dispensers had been inadvertently opened by the patients who mostly suffered from a concurrent corneal disease or a lesion on the corneal epithelium.
Closed-angle glaucoma: The immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil.
Muscle weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with diplopia, ptosis, and generalized weakness.
Brimonidine:
General
Although brimonidine tartrate 0.2% showed minimum effects on the blood pressure of patients enrolled in clinical studies, special precautions should be taken when treating patients with severe cardiovascular diseases.
Brimonidine has not been studied in individuals with liver or renal disorders; therefore, these patients should be treated cautiously.
BRIMOPRESS® T should be cautiously used in patients suffering from depression, cerebral or coronary failure, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
During the clinical studies, some loss of effect occurred in some patients. Brimonidine efficacy to lower the IOP observed during the first therapy month is not always equivalent to the long term reduction levels.
Carcinogenesis - Mutagenesis - Fertility disorders
Timolol maleate proved not to be mutagenic in-vivo in the micronucleous test and cytogenic test conducted in mice (doses greater than 800 mg/kg) and in-vitro in the neoplastic cell transformation assay (up to 100 mg/ml).
Fertility and reproduction studies in rats have not exhibited adverse effects in the fertility of female and male animals at doses greater than 21,000 times the systemic exposure resulting from the maximum recommended dose in human ophthalmology. No Brimonidine effects have been observed in the 21 month and 2 year studies in mice and rats to which oral doses of 2.5 mg/kg/day (as the free base) and 1.0 mg/kg/day, respectively (77 and 118 times, respectively, of the human plasma drug concentration with the recommended ophthalmic dose).
Brimonidine proved not to be either mutagenic or cytogenic in a course of in vitro and in vivo studies including the Ames test, host mediated assay, Chinese hamster ovary cell chromosome aberration (CHO), cytogenic studies in mice, and dominant lethal assay.
Pregnancy
Teratogenicity studies with Timolol conducted in mice, rats, and rabbits administered oral doses greater than 80 mg/kg/day (7000 times the systemic exposition of the maximum recommended dose in ophthalmology) did not show fetal malformations.
Reproduction studies conducted in rats with Brimonidine oral doses of 0.66 mg of base/kg did not show evidence of either fertility impairment or fetal damage. This dose level produced 100 times the plasma concentration observed in human beings with multiple ophthalmic doses.
Since no suitable studies with BRIMOPRESS® T in pregnant women, it should only be used during pregnancy if the potential benefit for the mother justifies the possible risk to the fetus.
Lactation
It is not known whether Brimonidine is excreted into human milk. Timolol maleate has been detected in breast milk after the drug oral and ophthalmic administration.
Due to the possibility of serious adverse reactions occurring in infants, lactation suspension or treatment interruption should be considered based on the significance of the product for the mother.
Pediatric use
The product safety and efficacy have not been determined in pediatric patients.
Interactions
Ocular interactions
When concomitant administration of eye drops containing adrenaline takes place, an ophthalmologic control is required (risk of mydriasis).
General interactions
Timolol:
Beta-adrenergic blocking agents: Patients concomitantly treated with oral beta-adrenergic blockers and BRIMOPRESS® T should be carefully monitored due to possible additive effect of the beta blocking action both at the intra-ocular and systemic pressure level. As a general rule, no two topical ophthalmic beta-adrenergic blockers should be concomitantly administered.
Calcium antagonists: Caution should be exercised when concomitantly administering beta-adrenergic blockers such as Timolol, and oral or intravenous calcium antagonists due to possible impairment of the atrio-ventricular conduction, left ventricular failure, and arterial hypotension. Concomitant administration of these drugs should be avoided in patients suffering from heart failure.
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.
Digitalics 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.
Quinidine: A potentiation of the beta blocking effect with the concomitant administration of Timolol and Quinidine has been reported, possibly because Quinidine inhibits the metabolism of Timolol via the Cytochrome P450.
Floctafenine: In case of shock or hypotension related to floctafenine, beta blockers decrease the cardiovascular compensatory response.
Sultopride: The bradycardic effect is added.
Amiodarone: Contractility, automatism, and conduction (suppression of compensatory sympathetic mechanisms) disorders.
Halogenated volatile anesthetics: Reduction of compensatory cardiovascular reactions due to the blocking effect.
Class I Anti-arrhythmics: Contractility, automatism, and conduction disorders (additive effect).
Baclofen: The hypotensive effect is facilitated.
Clonidine: Beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.
Insuline, oral hypoglicemic agents: Beta blockers can mask the hypoglycemic symptoms.
Lidocaine: Some beta blockers have been described to decrease the metabolism of lidocaine and therefore, its plasma concentration increases.
Iodine contrast media: In case of shock or hypotension due to iodine products, beta blockers reduce the compensatory cardiovasculars responses.
NSAIDs: Decrease of the hypotensive effect.
Tricyclic antidepressants, neuroleptics: Greater risk of orthostatic hypotension.
Corticoids: Decrease of the hypotensive effect.
Mefloquine: Risk of bradycardia (the bradycardic effect is added).
Brimonidine:
Although no specific interactions studies with BRIMOPRESS® T have been conducted, the possibility of an additive or potentiated effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.
In clinical studies, Brimonidine did not exhibit significant effects on either the pulse or the blood pressure. However, since alpha agonists, as a pharmacological class, can reduce the pulse and the blood pressure, caution should be exercised with the concomitant use of drugs such as beta blockers (ophthalmic or systemic use), antihypertensive drugs, and/or cardiotonic glycosides.
Tricyclic antidepressants have proved to attenuate the hypotensive effect of clonidine. It is not known whether the concomitant use of these agents with Brimonidine can lead to interference in the IOP reduction.
No data about the circulating catecholamine levels are available after administering BRIMOPRESS® T. However, caution is recommended in patients receiving tricyclic antidepressants, which may affect the metabolism and uptake of circulating amines.

Adverse reactions:
BRIMOPRESS® T (Brimonidine tartrate 0.2% and Timolol maleate as Timolol 0.5%) ophthalmic solution proved to be safe and well tolerated with an acceptable safety profile in clinical studies.
No adverse reactions due to the specific product combination were observed.
All the adverse reactions were previously reported, with different incidence, after the use of Brimonidine tartrate 0.2% or Timolol maleate as Timolol 0.5%.
In two clinical studies in which 385 patients were enrolled and treated with BRIMOPRESS® T for up to 12 months, the adverse reactions manifested in about 15% - 10% of patients included from greater to lower frequency the following: conjunctival hyperemia and burning sensation.
The adverse events manifested in about 9% - 4% of patients included from greater to lower frequency the following: pricking sensation, ocular pruritus, allergic conjunctivitis, and conjunctival folliculosis.
The following adverse reactions were reported in less than 4% of patients from greater to lower frequency: blurred vision, epiphora, ocular dryness, superficial punctate keratitis, erythema of eyelid, blepharitis, ocular drainage, eyelid edema, corneal erosion, ocular pain, sensation of foreign body, conjunctival edema, and follicular conjunctivitis.
The adverse reactions informed while using any product components and which might cause adverse reactions while using BRIMOPRESS® T are:
Brimonidine tartrate: The adverse events with incidence ≥ 1% - < 8% of patients treated with Brimonidine tartrate 0.2% ophthalmic solution included: vertigo, upper respiratory tract symptoms, gastrointestinal symptoms, abnormal taste, nasal dryness, photophobia, tearing, conjunctival edema, color loss of the conjunctiva, conjunctival pupils, and abnormal vision.
Timolol maleate: The adverse reactions informed while using Timolol maleate were: Cardiovascular adverse reactions: worsening or progress of certain cardiovasculars, pulmonary, and other disorders possibly related to the use of systemic beta blockers: bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, brain ischemia, palpitations, cardiac arrest, edema, claudication, Raynaud's phenomenon, cold sensation in hands and feet, congestive heart failure. Endocrine adverse reactions: masking of symptoms of hypoglycemia in insulin-dependent patients. Respiratory adverse reactions: bronchospasm (mainly in patients with pre-existing bronchospasm related diseases), respiratory insufficiency, dyspnea, cough. General adverse reactions: chest pain, fatigue. Nervous system/psychiatric adverse reactions: increase in signs and symptoms of myasthenia gravis, paresthesia, insomnia, nightmares, memory loss. Skin adverse reactions: alopecia, rash similar to psoriasis or exacerbation of psoriasis. Hypersensitivity adverse reactions: signs and symptoms of allergic reactions, including angioedema, hives, localized and generalized rash. Immunological adverse reactions: systemic lupus erythematosus. Digestive adverse reactions: nausea, diarrhea, dyspepsia. Special senses adverse reactions: decrease of the corneal sensitivity, visual impairment including refractive changes (sometimes due to interruption of miotic therapies), diplopia, ptosis, choroid detachment after filtering surgery, tinnitus. Urogenital adverse reactions: decreased libido, Peyronie's disease.
Adverse reactions of unknown causal relationship: the following adverse reactions were reported even though their causal relationship to the use of Timolol maleate has not been established: aphakial cystic macular edema, nasal congestion, anorexia, effects on the central nervous system (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychiatric disorders), hypertension, retroperitoneal fibrosis and pseudopemphigoid.
Laboratory clinical analyses: clinically significant changes in the laboratory standard parameters were rarely associated to the systemic administration of Timolol maleate. The following changes were recorded: mild increase in the level of blood urea nitrogen, potassium, uric acid, and triglycerides; and mild decrease in the level of hemoglobin, hematocrit, and HDL cholesterol; however theses changes did not progress and were not related to clinical manifestations. .
Timolol maleate (systemic formulation): The adverse reactions reported after the administration of oral Timolol maleate can be considered as potential adverse events for the ophthalmic route of administration.
Report of severe adverse reactions in pediatric patients: Severe adverse reactions related to the administration of Brimonidine tartrate 0.2% ophthalmic solution have been reported in pediatric patients (at ages from 28 days and 3 months). These reactions included: bradycardia, hypotension, hypothermia, hypotonia, apnea, dyspnea, hypoventilation, cyanosis, and lethargy resulting in hospitalization. After discontinuation of Brimonidine tartrate 0.2%, the pediatric patients recovered without sequelae.

Symptoms and treatment for overdose:
No information about BRIMOPRESS® T (Brimonidine tartrate 0.2% and Timolol maleate as Timolol 0.5%) ophthalmic solution overdose in human beings is available.
Cases of overdose with Timolol maleate ophthalmic solution have been reported with manifestations similar to the ones observed with beta blockers such as: vertigo, headache, dyspnea, bradycardia, bronchospasm, and cardiac arrest.
Treatment for an oral overdose includes supportive and symptomatic therapy. The airways should be kept open. Stomach emptying should be considered during the first overdose hours.
A study conducted in patients with renal impairment showed that Timolol maleate is not easily removed by dialysis.
Therapeutic measures for the overdose of Timolol maleate:
- ***Gastric lavage:*** when ingested.
- ***Symptomatic bradycardia:*** Administer atropine sulfate at a dose of 0.25 to 2 mg by intravenous route to induce vagal obstruction. If bradycardia persists, isoproterenol hydrochloride by intravenous route should be administered with caution. In refractory cases, the use of a transvenous cardiac pacemaker should be considered.
- ***Hypotension:*** Administer a sympathicomimetic hypertensive drug such as dopamine, dobutamine, or levarterenol. In refractory cases, glucagon hydrochloride can be used.
- ***Bronchospasm:*** Use isoproterenol hydrochloride. Additional treatment with aminophylline can be considered.
- ***Acute heart failure:*** Conventional treatment with digitalis, diuretics, and oxygen. In refractory cases, the administration of intravenous aminophylline is recommended. Later, if appropriate, glucagon hydrochloride can be administered.
- ***Cardiac obstruction (second or third degree):*** Use isoproterenol hydrochloride or transvenous cardiac pacemaker.

In case of overdosage, go to the nearest hospital or toxicology centers.

Information for patients:
Patients should be properly instructed to handle the dispenser tip avoiding the eye contact and contact with surrounding structures or any other surface. Improper handle of the dispenser may lead to its contamination causing ocular infections. Using contaminated products may cause severe ocular damage and the subsequent vision decrease.
The dispenser should be immediately closed after each instillation. Do not use the solution if the color changes or if turns cloudy. The unopened dispenser may be used until the expiration date printed in the box.

How supplied:
Drop bottle containing 5 ml of sterile ophthalmic solution.

Storage conditions:
Store below 30°C. Protect from light.

Once the package is first opened, it must be used within 4 weeks.

Keep medicaments out of the reach of children.

Delicate use product. To be administered under prescription and medical surveillance.

Manufactured by:
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