Other adverse reactions that have been reported with the individual components are listed below:.

Brimonidine tartrate: Abnormal taste; anxiety; blurring; conjunctival blanching; conjunctival edema; conjunctival hemorrhage; depression; dizziness; gastrointestinal symptoms; hypertension; insomnia; lid crusting; muscular pain; nasal dryness; pal pitations/arrhythmias; photophobia; syncope; and upper respiratory symptoms.

Timolol (ocular administration): Cardiovascular: arrythmia; bradycardia; cardiac arrest; cardiac failure; cerebral ischemia; cerebral vascular accident; claudication; cold hands and feet; edema; heart block; hypotension; palpitation; pulmonary edema; Raynaud's phenomenon: syncope; and worsening of angina pectoris, Digestive: anorexia Endocrine: masked symptoms of hypoglycemia in diabetes patients, (see **WARNINGS)** Hypersensitivity: signs and symptoms of systemic allergic reactions, including angioedema; urticaria; and generalized and localized rash Immunologic: systemic lupus erythematosus Nervous System/Psychiatric: increase in signs and symptoms of myasthenia gravis; somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss. Respiratory: bronchospasm (predominantly in patients with preexisting bronchospastic disease); respiratory failure, Skin: alopecia; exacerbation of psoriasis; psoriasiform rash Special Senses: choroidal detachment following filtration surgery (see **Precautions**); cystoid macular edema; decreased corneal sensitivity; pseudopemphigoid; ptosis; refractive changes; tinnitus, Urogenital: decreased libido; impotence; Peyronie's disease; retroperitoneal fibrosis.

OVERDOSAGE

No information is available on overdosage with **Combigan™** 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.

A study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **Combigan™** in the affected eye(s) twice daily. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 10 minutes apart.

HOW SUPPLIED: **Combigan™** is supplied sterile in 5 mL white plastic bottles.

NOTE: Store in a cool dark place.

Rx Only **9262X**

ALLERGAN

20700273 A 303/b

INSTRUCTIONS FOR USE उपयोग संबंधी निर्देश

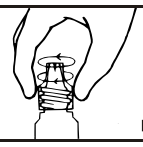


Fig. 1

Tighten the cap on the nozzle by turning it as shown. The spike in the cap will make a dispensing hole on the nozzle.

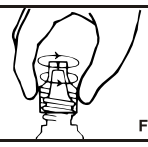


Fig. 2

Remove the cap, by turning it in the opposite direction.

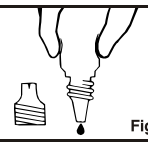


Fig. 3

The bottle is now ready for use; turn it up side down. Squeeze the walls of the bottle gently to deliver sterile drop into the eye.

ढक्कन को नोज़ल पर घुमाकर कस दें। ढक्कन में मौजूद कील से नोज़ल पर, दवा बाहर आने के लिए छिद्र बन जाएगा ।

विपरीत दिशा मे घुमाकर ढक्कन को निकालें ।

अब बोतल उपयोग के लिए तैयार है, उसे उल्टा करें, बोतल की दिवार को हलके से दबाएँ और आँखों में दवा की बूंदें डालें ।

Fig. 4

Replace the cap. Tighten it firmly and keep the bottle closed for subsequent use.

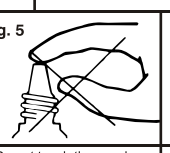


Fig. 5

Do not touch the nozzle.

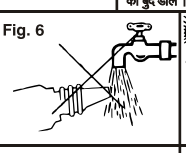


Fig. 6

Do not rinse the nozzle.

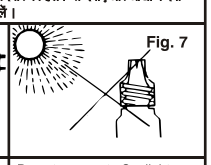


Fig. 7

Do not expose to Sunlight.

पुनः उपयोग में लाने तक ढक्कन को कसकर बोतल वापस बंद कर दें ।

बोतल के नोज़ल को हाथ न लगाएँ ।

नोज़ल को कभी न धोएं ।

बोतल को धूप में न रखें ।

State of the art technology
From Allergan India Private Limited

अत्याधुनिक तरीके से तैयार किया हुआ
अलरगन इंडिया प्राईवेट लिमिटेड द्वारा

BRIMONIDINE TARTRATE + TIMOLOL MALEATE OPHTHALMIC SOLUTION

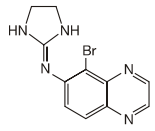
Combigan™

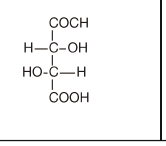
कॉम्बिगन

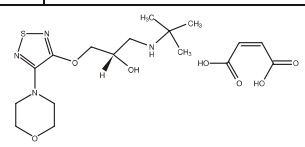
DESCRIPTION

Combigan™ (Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution) is a selective alpha-2 adrenergic agonist with a non-selective beta-adrenergic receptor blocking agent (topical antiglaucomatous agent).

	Brimonidine Tartrate	Timolol Maleate
Empirical Formula	$C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$	$C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$
Molecular Weight	442.24 as the tartrate salt	432.50 as the maleate salt
Chemical Name	5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate (1:1) (salt)	(-)-1-(tert-butylamino) -3-[(4-morpholino-1,2,5-thiadiazol -3-yl)-oxy]-2-propanol maleate
Appearance	Off-white, or white to pale-yellow powder	White, odorless, crystalline powder
Solubility	Soluble in both water (1.5 mg/mL) and in the product vehicle (3.0 mg/ml) at pH 7.2	Soluble in water, methanol, and alcohol.







In solution, **Combigan™** (Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution) 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.

Each mL of **Combigan™** contains:

Active ingredients:	Brimonidine Tartrate	2 mg
	Timolol Maleate IP equivalent to Timolol	5 mg
Preservative:	Benzalkonium Chloride IP/USNF	0.05 mg

Inactives: Sodium phosphate, monobasic; sodium phosphate, dibasic; purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action:

Combigan™ 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.

Combigan™ is a selective alpha-2 adrenergic agonist with a non-selective beta-adrenergic receptor blocking agent. 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 decreases aqueous humor production with little or no significant effect on episcleral venous pressure, outflow facility or uveoscleral outflow. Because timolol and brimonidine have different sites of action and different mechanisms by which they lower IOP, it is reasonable to expect that there will be an added IOP-lowering effect when the two are used adjunctively.

Timolol is a beta1 and beta2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

INDICATIONS AND USAGE

Combigan™ (brimonidine tartrate/ timolol ophthalmic solution) 0.2%/0.5% is indicated for reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who are insufficiently responsive to topical Beta Blockers.

Size : 220mm x 168mm
Color : Black

SHREE PRINTS			
	Artwork Code	Item Code	Leaflet
	A 303/b	20700273	Size : 220 x 168 mm (L x H) Open
	Prepared by		Date :
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CONTRAINDICATIONS

Combigan™ is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see **WARNINGS**); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see **WARNINGS**); (7) cardiogenic shock; (8) in patients receiving monoamine oxidase (MAO) inhibitor therapy; or (9) hypersensitivity to any component of this medication.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically. The same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of **Combigan™**. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol (see **CONTRAINDICATIONS**).

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, **Combigan™** 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 **Combigan™** is contraindicated [see **CONTRAINDICATIONS**]) should, in general, not receive beta-blocking agents, including **Combigan™**.

Major 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-adrenerg ic receptor blocking agents.

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

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., tachy cardia) 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.

Precautions:

General:

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.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. **Combigan™** has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g., timolol).

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.

Combigan™ has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Combigan™ should be used with caution in patients with depression, cerebral or coronary insuffuciency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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 (See Precautions, Information for Patients.).

Information for Patients:

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. (See CONTRAINDICATIONS.)

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See Precautions, General.)

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.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Patients should be advised that **Combigan™** contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of **Combigan™**.

As with other similar medications, **Combigan™** 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.

Drug Interactions:

Antihypertensives/cardiac glycosides: Because **Combigan™** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides is advised.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and **Combigan™** 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 coadministration of beta-adrenergic blocking agents, such as **Combigan™** and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration 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 **Combigan™** 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.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

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 **Combigan™** in humans can lead to resulting interference with the IOP lowering effect.

Pregnancy: 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 alimited extent. Because animal reproduction studies are not always predictive of human response, **Combigan™** 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 timolol or brimonidine tartrate 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:

Although safety and effectiveness of **Combigan™** in pediatric patients have not been established, brimonidine tartrate ophthalmic solution 0.2% was evaluated in a wellcontrolled clinical study in pediatric glaucoma patients (ages 2 to 7 years). In this study, brimonidine tartrate ophthalmic solution 0.2% was dosed t.i.d. as adjunctive therapy to beta-blockers. The most commonly observed adverse event in children was somnolence (55%). Reduced alertness was reported in 27% of children weighing 20 kg or less, and in 13% of children weighing over 20 kg. Approximately 13% of patients discontinued due to adverse experiences.

The safety and effectiveness of brimonidine tartrate ophthalmic solution 0.2% have not been studied in children below the age of 2 years. Brimonidine tarirate ophthalmic solution 0.2% 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.

Geriatric Use: No overall difference has been observed between elderly and other adult patients.

ADVERSE REACTIONS

Combigan™

In clinical trials, the most frequent events associated with the use of **Combigan™** occurring in approximately 5% to 10% of the patients included: conjunctival hyperemia; and ocular burning and stinging. The following adverse events were reported in 1 % to 5% of patients: allergic conjunctivitis; asthenia; blepharitis; conjunctival folliculosis; corneal erosion; epiphora; eye discharge; eye dryness; eye pain; eye pruritus; eyelid edema; eyelid erythema; foreign body sensation; headache; oral dryness; somnolence, superficial punctate keratitis; and visual disturbance.