PRODUCT MONOGRAPH

^{Pr}COMBIGAN®

(brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%)
Ophthalmic Solution

Relatively Selective α2-adrenoceptor Agonist and β-adrenergic Blocking Agent

Elevated Intraocular Pressure Therapy

Allergan Inc.
Markham, Ontario
L6G 0B5

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, brimonidine tartrate 0.2% /timolol maleate as timolol 0.5%	Contains 0.005% benzalkonium chloride as preservative *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

COMBIGAN® (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution is indicated for the control of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to IOP reducing monotherapy AND when the use of **COMBIGAN®** is considered appropriate.

COMBIGAN® is also indicated for reduction of long term fluctuation in IOP. In addition to controlling IOP, **COMBIGAN®** reduces long term variability, or fluctuation, in IOP. Together, reductions in IOP and in IOP fluctuation are expected to slow the progression of visual field loss in patients with glaucoma.

Diabetics:
Results from pivotal trials indicate that the mean change from baseline IOP was significantly lower ($p < 0.001$) with **COMBIGAN®** than with either brimonidine tartrate alone or timolol maleate alone for both patients with diabetes and those without diabetes. See Warnings and Precautions for considerations during use in this population.

Patients using Systemic Beta-blockers:
Results from pivotal trials indicate that the mean change from baseline IOP was significantly lower ($p < 0.001$) with **COMBIGAN®** than with either brimonidine tartrate alone or timolol maleate alone for both patients treated with systemic beta blockers and those who were not. Topical beta-blockers are known to be less effective in patients on systemic beta-blockers. See Drug Interactions. This analysis shows that this is not the case with **COMBIGAN®**, despite

having timolol as one of the ingredients.

Geriatrics (> 65 years of age):
Based on evidence from clinical studies and experience, use in the geriatric population is not associated with any differences in safety or effectiveness. Use as is for adult patients.

Paediatrics (< 18 years of age):
Not recommended for paediatric use. The safety and efficacy of **COMBIGAN®** in paediatric patients have not been established in clinical trials.

CONTRAINDICATIONS

NOTE: COMBIGAN® is a combination of brimonidine tartrate 0.2% and timolol 0.5% as timolol maleate. When **COMBIGAN®** is prescribed, the relevant Product Monographs for brimonidine tartrate and/or timolol maleate should be consulted.

- Patients who are hypersensitive to brimonidine tartrate, timolol maleate or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Patients with reactive airway disease including bronchial asthma or a history of bronchial asthma; severe chronic obstructive pulmonary disease
- Patients with sinus bradycardia; sick sinus syndrome; sino-atrial nodal block; second- or third-degree atrioventricular block not controlled with a pacemaker; overt cardiac failure; cardiogenic shock
- Patients receiving monoamine oxidase (MAO) inhibitor therapy
- Neonates and infants (children under the age of 2 years; see ADVERSE REACTIONS, *Brimonidine Tartrate*)

WARNINGS AND PRECAUTIONS

General
NOTE: COMBIGAN® is a combination of brimonidine tartrate 0.2% and timolol 0.5% as timolol maleate. When **COMBIGAN®** is prescribed, the relevant Product Monographs for brimonidine tartrate and/or timolol maleate should be consulted.

FOR TOPICAL OPHTHALMIC USE ONLY.

If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

As with many topically applied ophthalmic drugs, the active substances (brimonidine tartrate and timolol) in **COMBIGAN®** may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution. 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 maleate. See Contraindications.

Carcinogenesis and Mutagenesis
See Toxicology**.**

Cardiovascular
Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with **COMBIGAN®**. In patients with a history of severe cardiac disease, coronary heart disease, Prinzmetal's angina, signs of cardiac failure should be watched for and pulse rates should be checked.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Caution should be exercised in treating patients with severe cardiovascular disease.

Use with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or *thromboangiitis obliterans.*

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with **COMBIGAN®**, alternative therapy should be considered.

Endocrine and Metabolism
Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemia agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycaemia.

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Hepatic/Biliary/Pancreatic
COMBIGAN® has not been studied in patients with hepatic impairment; caution should be exercised in treating such patients.

Musculoskeletal
Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). Timolol maleate has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Ophthalmologic
COMBIGAN® should not be used alone in the treatment of acute angle-closure glaucoma.

COMBIGAN® contains the preservative benzalkonium chloride, which may be absorbed by and cause discoloration of soft contact lenses.

The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Choroidal detachment after filtration procedures has been reported with administration of aqueous suppressant therapy (e.g., timolol maleate, acetazolamide). Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

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.

Corneal diseases: Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Peri-Operative Considerations
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anesthetics. The anesthetist must be informed if the patient is using **COMBIGAN®**.

Psychiatric
COMBIGAN® should be used with caution in patients with depression.

Renal
COMBIGAN® has not been studied in patients with renal impairment; caution should be exercised in treating such patients.

Respiratory
Patients with chronic obstructive pulmonary disease of mild or moderate severity should, in general, not receive products containing beta-blockers, including **COMBIGAN®**; however, if **COMBIGAN®** is deemed necessary in such patients, it should be administered with caution.

Sensitivity/Resistance
Because of the brimonidine tartrate component **COMBIGAN®** should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists.

Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solution 0.2%, with some reported to be associated with an increase in IOP.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. These patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions since timolol maleate may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of **COMBIGAN®** in pregnant women. 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.

There has been no experience with exposure during pregnancy in clinical trials.

Nursing Women: Timolol maleate 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 maleate 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.

Pediatrics (< 18 years of age): The use of **COMBIGAN®** in pediatric patients is currently not recommended (see CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Occupational Hazards

COMBIGAN®, as with other similar medications, can potentially 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. **COMBIGAN®** may also cause blurred vision or visual disturbance upon instillation. The patient should wait until these symptoms have cleared before driving or using machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Based on 12 month clinical data, the most commonly reported adverse drug reactions were conjunctival hyperaemia (approximately 15% of patients) and burning sensation in the eye (approximately 11% of patients). The majority of cases were mild and led to discontinuation

rates of only 3.4% and 0.5% respectively.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials, **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution was safe and well tolerated and had an acceptable safety profile. No adverse reactions unique to the combination product have been observed. All adverse reactions have been previously reported for brimonidine tartrate 0.2% or timolol maleate as timolol 0.5%, though at different incidences.

In two clinical studies including 385 patients treated with **COMBIGAN®** for up to 12 months, treatment-related adverse reactions reported (pooled analysis) occurring at ≥1% with **COMBIGAN®** are presented in Table 1 below.

Table 1 - Treatment Related Adverse Reactions Occurring at ≥1% with COMBIGAN®

System Organ Class Preferred Term[a]	Combination N = 385	Brimonidine Tartrate N = 382	Timolol Maleate N = 392
General disorders and administration site conditions			
asthenia	8 (2.1%)	16 (4.2%)	3 (0.8%)
Gastrointestinal disorders			
oral dryness	8 (2.1%)	35 (9.2%)[b]	2 (0.5%)
Nervous system disorders			
somnolence	6 (1.6%)	14 (3.7%)	2 (0.5%)
headache	4 (1.0%)	13 (3.4%)[b]	4 (1.0%)
Eye disorders			
conjunctival hyperaemia	56 (14.5%)	87 (22.8%)[b]	29 (7.4%)[c]
burning sensation in eye	42 (10.9%)	28 (7.3%)	53 (13.5%)
stinging sensation eye	24 (6.2%)	11 (2.9%)[c]	26 (6.6%)
eye pruritus	21 (5.5%)	42 (11.0%)[b]	11 (2.8%)
allergic conjunctivitis	20 (5.2%)	36 (9.4%)[b]	1 (0.3%)[c]
conjunctival folliculosis	19 (4.9%)	35 (9.2%)[b]	7 (1.8%)[c]
visual disturbance (blurred vision)	14 (3.6%)	16 (4.2%)	12 (3.1%)
epiphora	12 (3.1%)	19 (5.0%)	5 (1.3%)
eye dryness	12 (3.1%)	13 (3.4%)	4 (1.0%)[c]
superficial punctate keratitis	12 (3.1%)	5 (1.3%)	4 (1.0%)[c]
erythema eyelid	11 (2.9%)	12 (3.1%)	4 (1.0%)
blepharitis	11 (2.9%)	11 (2.9%)	2 (0.5%)[c]
eye discharge	10 (2.6%)	7 (1.8%)	3 (0.8%)[c]
eyelid edema	10 (2.6%)	6 (1.6%)	2 (0.5%)[c]
corneal erosion	10 (2.6%)	5 (1.3%)	11 (2.8%)
eye pain	6 (1.6%)	10 (2.6%)	6 (1.5%)
irritation eye	6 (1.6%)	3 (0.8%)	5 (1.3%)
foreign body sensation	5 (1.3%)	17 (4.5%)[b]	7 (1.8%)
eyelids pruritus	4 (1.0%)	3 (0.8%)	0 (0.0%)

Table 1 - Treatment Related Adverse Reactions Occurring at ≥1% with COMBIGAN®

System Organ Class Preferred Term[a]	Combination N = 385	Brimonidine Tartrate N = 382	Timolol Maleate N = 392
Psychiatric disorders			
depression	4 (1.0%)	3 (0.8%)	1 (0.3%)
Vascular disorders			
hypertension	4 (1.0%)	1 (0.3%)	1 (0.3%)

a MedDRA System Organ Class and Preferred Terms
b incidence with the Combination was significantly lower than with monotherapy ($p \leq .05$)
c incidence with the Combination was significantly higher than with monotherapy ($p \leq .05$)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiac disorders: congestive heart failure, palpitations
Gastrointestinal disorders: taste perversion, diarrhea, nausea
Nervous system disorders: dizziness, syncope
Respiratory, thoracic and mediastinal disorders: rhinitis, nasal dryness
Skin and subcutaneous tissue disorders: allergic contact dermatitis
Eye disorders: visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment

Abnormal Haematologic and Clinical Chemistry Findings

Common: Liver function tests abnormal

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during postmarketing use of **COMBIGAN®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac disorders: bradycardia
Skin and subcutaneous tissue disorders: erythema facial

Additional adverse events that have been reported with one of the components and may be potential adverse reactions for **COMBIGAN®** are:

Brimonidine tartrate:

Adverse events reported in ≥1% and < 8% of patients receiving ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% include: Dizziness, upper respiratory symptoms, gastrointestinal symptoms, abnormal taste, nasal dryness, photophobia, tearing, conjunctival edema, conjunctival blanching, conjunctival papillae, and abnormal vision, tachycardia, hypersensitivity, skin reaction (including erythema, face edema, pruritus, rash, and vasodilatation).

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with Alphagan as adjunctive treatment. In 8% of children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-year-

old age group (25%), but was more affected by weight, occurring more frequently in those children weighing ≤20 kg (63%) compared to those weighing >20 kg (25%).

The safety and effectiveness of brimonidine tartrate ophthalmic solution has not been studied in children under the age of two years. During post-marketing surveillance somnolence, lethargy, hypotonia, hypothermia, bradycardia, hypotension, apnoea, respiratory depression, pallor and coma have been reported in neonates, infants and children receiving brimonidine either for congenital glaucoma or via accidental ingestion.

For other detailed information, please consult the Product Monograph for brimonidine tartrate.

Timolol maleate:
Adverse events reported with timolol maleate include:
Cardiac disorders: Aggravation or precipitation of certain cardiovascular, pulmonary, and other disorders presumably related to effects of systemic beta blockade (see Contraindications, Warnings and Precautions), including bradycardia; arrhythmia; heart block; atrioventricular block; cerebrovascular accident; cerebral ischemia; palpitations; chest pain; cardiac arrest; edema; congestive heart failure, cardiac failure; pulmonary oedema; worsening of angina pectoris.
Metabolism and nutrition disorders: masked symptoms of hypoglycaemia in insulin-dependent diabetics.
Respiratory, thoracic and mediastinal disorders: bronchospasm (predominantly in patients with pre-existing bronchospastic disease); respiratory failure; dyspnea; cough; upper respiratory infection.
General disorders and administration site conditions: fatigue.
Nervous system disorders: increase in signs and symptoms of myasthenia gravis; paresthesia; syncope; cerebrovascular accident; cerebral ischemia; dizziness and headache.
Skin and subcutaneous tissue disorders: alopecia; psoriasiform rash or exacerbation of psoriasis; skin rash.
Immune system disorders: signs and symptoms of allergic reactions including anaphylaxis, angioedema, localized and generalized rash, pruritus, urticaria; systemic lupus erythematous, hypersensitivity.
Gastrointestinal disorders: nausea; diarrhea, dyspepsia; abdominal pain; dysgeusia; vomiting; dry mouth.
Musculoskeletal and connective tissue disorders: myalgia.
Eye disorders: decreased corneal sensitivity; visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases); diplopia; ptosis; choroidal detachment following filtration surgery; refractive changes, conjunctivitis; blepharitis; keratitis; vision blurred.
Ear and labyrinth disorders: tinnitus.
Reproductive system and breast disorders: decreased libido; Peyronie's disease, sexual dysfunction.
Vascular disorders: claudication; cold hands and feet; hypotension: Raynaud's phenomenon.
Psychiatric disorders: insomnia, memory loss, nightmares, depression.

Causal Relationship Unknown
The following adverse reactions have been reported but a causal relationship to therapy with timolol maleate has not been established: aphakic cystoid macular edema, nasal congestion, anorexia, CNS effects (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid.

Timolol maleate (systemic formulation):
Adverse reactions reported in clinical experience with oral timolol maleate may be considered potential side effects of ophthalmic timolol maleate.

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in blood urea nitrogen, serum potassium and serum uric acid and triglycerides, and slight decreases in hemoglobin and hematocrit and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

For other detailed information, please consult the Product Monograph for timolol maleate.

DRUG INTERACTIONS

No interaction studies have been performed with **COMBIGAN®**.

Beta-adrenergic Blockers
Patients who are receiving a beta-adrenergic blocking agent orally and **COMBIGAN®** should be closely observed for potential additive effects of beta-blockade, both systemically and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Anti-hypertensives/Cardiac glycosides
There is the potential for additive effects resulting in hypotension, and/or marked bradycardia when beta-blocker eye drops are administered concomitantly with oral calcium channel blockers, anti-arrythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine, and other anti-hypertensives.

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.

Epinephrine
Mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.

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

Clonidine
Oral 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.

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®** can lead to an interference in IOP lowering effect.

No data are available on the level of circulating catecholamines after **COMBIGAN®** is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Although specific drug interaction studies have not been conducted with **COMBIGAN®**, the possibility of an additive or potentiating effect with CNS depressants such as alcohol exists.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dose is one drop of **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution in the affected eye(s) twice daily (doses taken approximately 12 hours apart).

Missed Dose
A missed dose should be applied as soon as the patient remembers. The regular dosing schedule should then be resumed with the next dose.

Administration

As with any eye drops, it is recommended that the lachrymal sac be compressed at the medial canthus (punctual occlusion) for one minute, to reduce possible systemic absorption. This should be performed immediately following the instillation of each drop.

If more than one topical ophthalmic product is to be used, the different products should be instilled at least 10 minutes apart.

The preservative in **COMBIGAN®**, benzalkonium chloride, may be absorbed by soft (hydrophilic) contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling **COMBIGAN®** to insert soft contact lenses.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops. If handled improperly, ocular solutions 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.

OVERDOSAGE

In case of a suspected overdose, including accidental oral ingestion, contact your regional poison control centre.

There is limited data available of overdosage in humans with the use of **COMBIGAN®**. Bradycardia has been reported in association with use of a higher than recommended dose. If overdosage occurs, treatment should be symptomatic and supportive; a patent airway should be maintained.

There have been reports of inadvertent overdoses with timolol maleate 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, cardiac arrest.

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Evacuation of the stomach should be considered during the first few hours after an overdose.

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

Specific therapeutic measures for the treatment of overdose with timolol maleate are reproduced below for ease of reference:

Gastric Lavage: If ingested.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.

Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

COMBIGAN® (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution reduces intraocular pressure (IOP) by reducing aqueous humor production and increasing uveoscleral outflow.

COMBIGAN® is a combination product containing brimonidine tartrate and timolol maleate. Individually, each of these components is used to control IOP in humans.

Brimonidine tartrate is a relatively selective alpha adrenergic receptor agonist that in radioligand binding assays and in functional assays, is approximately 1000 times more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor. This selectivity results in the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. Brimonidine tartrate lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow.

Timolol maleate is a general beta-adrenergic receptor blocking agent that combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biological response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or

exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of agonist, which will restore the usual biologic response.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous humor formation.

Both brimonidine tartrate and timolol maleate have a rapid onset of action, with the peak ocular hypotensive effect occurring at approximately two hours post-dosing for brimonidine tartrate and one to two hours for timolol maleate. The duration of effect is 12 hours or greater for brimonidine tartrate and 24 hours for timolol maleate.

Pharmacodynamics

The topical administration of brimonidine tartrate 0.2% ophthalmic solution decreases intraocular pressure (IOP) with minimal effect on cardiovascular parameters. Brimonidine tartrate 0.2% has no effect on pulmonary function or exercise-induced tachycardia. The cardiovascular effects of brimonidine tartrate 0.2% during exercise in normal volunteers were found to be limited to a slight suppression of systolic blood pressure, which was clinically insignificant, during the recovery period following a treadmill test.

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

Pharmacokinetics

Absorption: Plasma brimonidine tartrate and timolol maleate concentrations were determined in 16 healthy subjects dosed with **COMBIGAN®** , ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2%, or TIMOPTIC® (timolol maleate) ophthalmic solution USP 0.5%, each BID for seven days in a three-period, complete crossover study. There were no statistically significant differences in brimonidine tartrate or timolol maleate AUC between **COMBIGAN®** and the respective monotherapy treatments. Mean plasma brimonidine tartrate C_{max} values from the **COMBIGAN®** and ALPHAGAN® 0.2% groups were 0.0327 ± 0.0150 (N = 15) and 0.0347 ± 0.0226 ng/mL (N = 16), respectively, indicating no apparent difference. Mean plasma timolol maleate C_{max} values from the **COMBIGAN®** and TIMOPTIC® USP 0.5% treatment groups were 0.406 ± 0.216 (N = 15) and 0.507 ± 0.269 ng/mL (N = 14), respectively. Although the C_{max} of timolol maleate was approximately 20% lower in the **COMBIGAN®** treatment, the difference was not statistically significant (p=0.088).

Therapeutic drug monitoring was conducted in the two Phase 3 trials. Brimonidine tartrate and timolol maleate plasma concentrations from the **COMBIGAN®** BID group were 15-49% lower than their respective monotherapy values. In the case of brimonidine tartrate, the difference appears to be due to BID dosing for **COMBIGAN®** and TID dosing for ALPHAGAN®.

The lower timolol maleate plasma concentrations seen with **COMBIGAN®**, as compared to timolol maleate 0.5%, appear to be related to a slower absorption of timolol maleate, which may be due to a difference in the benzalkonium concentrations rather than a drug-drug (brimonidine tartrate-timolol maleate) interaction.

Orally administered timolol maleate is rapidly and nearly completely absorbed (~90% availability). The apparent elimination half-life of timolol maleate in plasma is 4 hours. The half-life is essentially unchanged in patients with moderate renal insufficiency.

Metabolism: Timolol maleate is partially metabolized by the liver and timolol maleate and its metabolites are excreted by the kidney. Timolol maleate is not extensively bound to plasma proteins (~ 60%). After oral dosing, timolol maleate is subject to moderate first-pass metabolism (~50%). Only a small amount of unchanged drug appears in the urine, along with its metabolites after oral dosing.

Excretion: In humans, brimonidine tartrate is eliminated rapidly via extensive systemic metabolism; there is no marked systemic accumulation after multiple dosing. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine in the first 96 hours.

STORAGE AND STABILITY

COMBIGAN® (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution should be stored at room temperature (15°C to 25°C). Protect from light.

Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

Ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can be 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution contains brimonidine tartrate 2.0 mg and timolol maleate 5.0 mg with the following non-medicinal ingredients: 0.005% benzalkonium chloride as preservative; sodium phosphate, monobasic monohydrate; sodium phosphate, dibasic heptahydrate; purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

COMBIGAN® is supplied in white, opaque plastic dropper bottles containing: 2.5 mL, and 10 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Brimonidine Tartrate

Proper name: brimonidine tartrate

Chemical name: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate

Molecular formula and molecular mass: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$; 442.24

Structural formula:

Physicochemical properties: Brimonidine tartrate is an off-white, pale yellow to pale pink powder, with a melting point range of 202 - 210°C. It is water soluble (34 mg/mL) and soluble in DMSO (>60 mg/mL), slightly soluble in propylene glycol (~1.0 mg/mL), and very slightly soluble in ethanol (0.6 mg/mL) and acetone (<0.2 mg/mL). The pH of a 1% solution of brimonidine tartrate in water is 3.5 at room temperature. A pK_a value of 7.78 ± 0.05 has been determined.

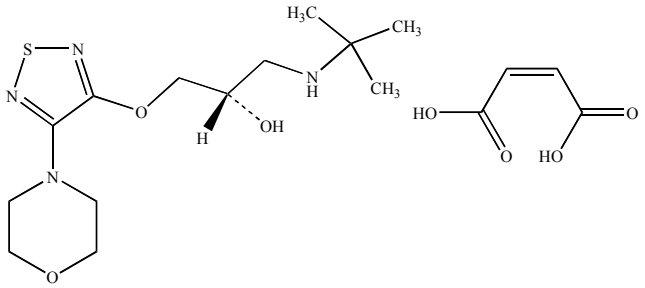
Timolol Maleate

Proper name: timolol maleate

Chemical name: (-)-1-(tert-butylamino]-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1) (salt)

Molecular formula and molecular mass: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$; 432.50

Structural formula:



Physicochemical properties: Timolol maleate is a white odourless, crystalline powder which is soluble in water, methanol and alcohol and has a melting point of 201.5°C to 202.5°C.

CLINICAL TRIALS

Three clinical trials evaluating the safety and efficacy of **COMBIGAN®** in the treatment of patients with glaucoma or ocular hypertension have been performed.

A phase 2 study (N=73) was conducted to evaluate the safety, efficacy and tolerability of **COMBIGAN®** dosed twice-daily, compared with brimonidine tartrate 0.2% dosed three-times-daily and timolol maleate 0.5% dosed twice-daily, each administered for 7 days. The study demonstrated that the short-term dosing with **COMBIGAN®** was well tolerated with a safety profile similar to timolol maleate and to brimonidine tartrate, and provided statistically significant and clinically relevant reduction of IOP of up to 7.8 mm Hg from baseline in patients with glaucoma or ocular hypertension.

Two 12-month clinical studies (N=1,159) were conducted to determine the efficacy and safety of **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution administered BID compared with brimonidine tartrate 0.2% administered TID and timolol maleate 0.5% administered BID in patients with glaucoma or ocular hypertension.

Study demographics and trial design

Table 2 - Summary of Patient Demographics for Clinical Trials in the Treatment of Elevated IOP in Patients with Glaucoma or Ocular Hypertension

Study #	Trial design	Dosage, route of administration and duration	Subjects (N)	Mean age (Range)	Gender
190342-012T	Randomized, Double-blind, Parallel Group, Active Control	One drop in each affected eye. COMBIGAN: BID Timolol maleate 0.5%:BID Brimonidine tartrate 0.2% TID Ocular 12 Months	573 enrolled 192 195 186 (497 completed 3 mo; 407 completed 12 mo)	62.8 years (32 to 89)	M: 43.3% (248/573) F: 56.7% (325/573)
190342-013T	Randomized, Double-blind, Parallel Group, Active Control	One drop in each affected eye. COMBIGAN: BID Timolol maleate 0.5%:BID Brimonidine tartrate 0.2% TID Ocular 12 Months	586 enrolled 193 197 196 (502 completed 3 mo; 426 completed 12 mo)	62.4 years (23 to 87)	M: 46.1% (270/586) F: 53.9% (316/586)

The study population included adult subjects diagnosed with ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma. Primary inclusion criteria were post-washout morning IOP (Baseline, Hour 0) of at least 22 mm Hg and no higher than 34 mm Hg in each eye, asymmetry of IOP not greater than 5 mm Hg, and best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.

Study results

During the 12-month treatment period, the greater IOP lowering effect of **COMBIGAN®** BID was demonstrated throughout the day, and this effect was maintained during the 12 months treatment period. Furthermore, analysis of the long-term safety data showed that **COMBIGAN®** had an acceptable safety profile, and that adverse experiences were limited to those that were reported previously with ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2% and/or timolol maleate ophthalmic solution 0.5%.

The efficacy results (pooled analysis) from the two 12 month clinical trials are presented in Table 3 below:

Table 3 - Results of Studies -012T and -013T; Treatment of Elevated IOP in Patients with Glaucoma or Ocular Hypertension

Primary Endpoints	Statistical significance for COMBIGAN™ versus Brimonidine Tartrate	Statistical significance for COMBIGAN™ versus Timolol Maleate
Mean IOP (hours 0, 2, 7, and 9) at Weeks 2, 6, Months 3, 6, 9, (Hours 0 and 2 only), Month 12; pooled data from Studies 190342-012T and 190342-013T	Mean IOP was significantly lower with the **COMBIGAN™** than with brimonidine tartrate TID at Hours 0, 2, 7, and 9 at all follow-up visits ($p \leq 0.018$) except for Week 2, Hour 9 ($p=0.093$)	Mean IOP was significantly lower with the **COMBIGAN™** than with timolol maleate at hours 0, 2, 7, and 9 at all follow-up visits ($p < 0.001$)

Supplemental analyses of pooled Studies 190342-012T and 190342-013T demonstrated that **COMBIGAN®** was clinically and statistically more effective both in lowering IOP and in stabilizing IOP fluctuation than either brimonidine tartrate administered TID or timolol maleate administered BID.

Table 4 - Proportion of Patients with Daily IOP SD Fluctuation Less Than 3 mmHg and Mean IOP Less than 18 mmHg (Pooled 12-Month Studies 012T and 013T)

Visit	COMBIGAN N=384	Brimonidine Tartrate N=381	Timolol Maleate N=392	COMBIGAN vs. Brim p-value[a]	COMBIGAN vs. Timolol p-value[a]
Week 2	64.5%	28.8%	45.6%	< 0.001	< 0.001
Week 6	65.5%	32.0%	48.8%	< 0.001	< 0.001
Month 3	64.1%	33.1%	44.8%	< 0.001	< 0.001
Month 6	61.7%	27.0%	43.1%	< 0.001	< 0.001
Month 9	49.5%	23.5%	34.7%	< 0.001	< 0.001
Month 12	58.1%	31.6%	41.2%	< 0.001	< 0.001

Note: Daily fluctuation is the standard deviation at the visit. Patients with complete data for the visit are included. Mean IOP is the mean diurnal IOP for the specified visit

[a] P-value for the between-group comparison at each visit is based on Chi-Square

Table 5 - Proportion of Patients with Hourly IOP SD Fluctuation Less Than 3 mmHg and Mean IOP Less than 18 mmHg (Pooled 12-Month Studies 012T and 013T)

Visit	COMBIGAN N=288	Brimonidine Tartrate N=213	Timolol Maleate N=327	COMBIGAN vs. Brim p-value[a]	COMBIGAN vs. Timolol p-value[a]
Hour 0	145/288 (50.3%)	32/213 (15.0%)	112/325 (34.5%)	< 0.001	<0.001
Hour 2	215/279 (77.1%)	107/211 (50.7%)	156/321 (48.6%)	< 0.001	<0.001
Hour 7	177/281 (63.0%)	70/207 (33.8%)	160/322 (49.7%)	< 0.001	0.001
Hour 9	180/278 (64.7%)	121/204 (59.3%)	161/315 (51.1%)	0.223	<0.001

Note: Hourly fluctuation is the standard deviation at that hour across all visits. Patients with data at each visit for the given hour are included. Mean IOP is the mean of the IOPs at all visits for the specified hour.

[a] P-value for the between-group comparison at each visit is based on Chi-Square

In a supplemental analysis of a subgroup of patients receiving systemic beta-blockers in the pooled studies, the mean change from baseline IOP was significantly lower ($p < 0.001$) with **COMBIGAN®** than with either brimonidine tartrate TID or timolol maleate administered BID. There was no statistically significant difference in IOP reduction between patients receiving beta

blockers and those who were not for patients who were treated with **COMBIGAN®** (-6.2 mm Hg vs. -6.2 mm Hg, p = 0.920) or with brimonidine tartrate (-3.7 mm Hg vs. -4.1 mm Hg, p = 0.400). However, patients treated with timolol maleate who were also receiving concomitant systemic beta blockers had a significantly smaller reduction in IOP than those who were not treated with a concomitant beta-blocker (-3.8 mm Hg versus -4.9 mm Hg, p = 0.007)**.**

A supplemental analysis of a subgroup of diabetic and non-diabetic patients was also performed on the pooled data. Mean change from baseline IOP with **COMBIGAN®** was significantly lower (p < 0.001) with than either brimonidine tartrate or timolol maleate for both diabetics and non-diabetics. For patients with diabetes mellitus, there was no statistically significant difference in IOP reduction from baseline in comparison to non-diabetic patients following treatment with **COMBIGAN®** (-5.9 mm Hg vs. -6.3 mm Hg, p = 0.241). With brimonidine tartrate treatment however, diabetic patients had a significantly smaller IOP reduction effect than non-diabetics (-3.3 mm Hg vs. -4.2 mm Hg, p = 0.003). Similarly, with timolol maleate treatment, diabetic patients had a significantly smaller effect than non-diabetics (-4.1 mm Hg vs. -5.0 mm Hg, p = 0.004).

In the Phase 3 studies, heart rate was measured at pre-study, baseline, and each follow-up visit at Hour 0 (pre-dose) and Hour 2 (post-dose). In each study, small but statistically significant mean decreases from baseline with **COMBIGAN®** were similar to those with timolol maleate. Mean decreases were significantly greater with **COMBIGAN®** than with brimonidine tartrate at Hour 2 for each follow-up visit in each study.

Systolic and diastolic blood pressure were measured at prestudy, baseline, and each follow-up visit at hour 0 (pre-dose) and hour 2 (post-dose). At hour 0 in each study, small within-group changes from baseline systolic blood pressure were generally not significant. At Hour 2, small but statistically significant mean decreases from baseline with **COMBIGAN®** were similar to those with brimonidine tartrate. There were no statistically significant differences between **COMBIGAN®** and either individual component in the mean change from baseline systolic blood pressure at any time point in either study.

At Hour 0 in each study, small within-group changes from baseline diastolic blood pressure were generally not significant. At Hour 2, small but statistically significant mean decreases from baseline with **COMBIGAN®** were similar to those with brimonidine tartrate. Mean decreases at Hour 2 were significantly greater with **COMBIGAN®** than with timolol maleate at each follow-up visit in each study. Generally, the differences in mean decrease in diastolic blood pressure between the **COMBIGAN®** and brimonidine tartrate groups were not significant.

DETAILED PHARMACOLOGY

Animal Pharmacology

Receptor binding and functional studies have characterized brimonidine tartrate as a potent and selective alpha-2-adrenoceptor agonist. As indicated in Table 6, brimonidine tartrate is notably more alpha-2 adrenoceptor selective than clonidine and *p*-aminoclonidine in both radioligand binding and functional assays.

Table 6 - Receptor Pharmacology of Brimonidine Tartrate, Clonidine and p-Aminoclonidine

Radioligand Binding; Ki (nM)*				Functional; EC_{50} (nM)*	
Compound	**Alpha-1[a]**	**Alpha-2[b]**		**Alpha-1[c]**	**Alpha-2[d]**
Brimonidine Tartrate	1850 ± 322 (5)	1.9 ± 0.5 (6)		1490 ± 214 (12)	1.0 ± 0.1 (24)
Clonidine	513 ± 108 (4)	3.4 ± 0.4 (6)		293 ± 47 (4)	4.4 ± 0.4 (11)
p-Aminoclonidine	181 ± 18 (4)	7.8 ± 1.2 (2)		180 ± 10 (8)	1.9 ± 0.2 (9)

* Mean ± SEM; 'N' is noted in parentheses.
[a] [^{3}H]Prazosin in human cerebral cortex.
[b] [^{3}H]Rauwolscine binding in HT-29 cells.
[c] Contraction of isolated rabbit aorta.
[d] Inhibition of electrically induced contractions in the isolated rabbit vas deferens.

The ocular hypotensive effect of brimonidine tartrate has been demonstrated in normotensive rabbits, cats, and monkeys, as well as ocular hypertensive rabbits and monkeys. This effect is maintained following six months of chronic administration to albino rabbits (Table 7).

Table 7 - The IOP Response to Chronic Administration of Brimonidine Tartrate (BID for 6 months) in Rabbits

Concentration (%)[a]	Acute	Three Months	Six Months
0.08	4.3b*	5.1*	3.8*
0.2	4.0*	6.0*	5.1*
0.5	0.2	6.0*	6.9*
0.8	1.0	6.5*	7.1*

[a] Concentration based on the bitartrate salt
[b] Mean decrease in treated eye IOP (mm Hg) from vehicle-treated control at 2 hr following the AM dose.
* Significantly different from vehicle-treated animals ($p<0.05$) for treated eye

Twenty-eight days of BID dosing of brimonidine tartrate 0.5% to rabbits and monkeys demonstrated that monkeys experience a significantly diminished trough ocular hypotensive effect on chronic dosing. In rabbits, the trough IOP effect was unaltered, however, the peak effect significantly increased with this dosing regimen (confirmed also by 6 month experiments - see Table 7).

The mechanism of action for the ocular hypotensive effect of brimonidine tartrate in rabbits and monkeys is predominantly the suppression of aqueous humor production. Trabecular outflow was not found to be affected in monkeys. In rabbits, a secondary mechanism of action includes an enhancement of uveoscleral outflow.

Investigational studies have demonstrated that topically administered brimonidine tartrate stimulates a peripheral alpha-2 adrenoceptor to lower IOP in rabbits. SKF 104078, the selective postjunctional alpha-2 receptor antagonist, did not block the ocular hypotensive effects of brimonidine tartrate in rabbits, suggesting that the vascular postjunctional alpha-2 adrenoceptor is not involved in the IOP response in this species. The data in monkeys suggest that the IOP and cardiovascular responses to brimonidine tartrate are mediated by an imidazoline receptor located in the central nervous system (CNS). The miotic response to brimonidine tartrate which occurs in monkeys is mediated by an alpha-2 adrenoceptor.

When the action of brimonidine tartrate as a neuroprotective agent was evaluated in *in vitro* and *in vivo* pharmacological studies in rats, no deleterious effects on the optic nerve were observed.

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

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided.

Animal Pharmacokinetics

Brimonidine tartrate and timolol maleate are rapidly absorbed following single or multiple instillation of ophthalmic solutions in rabbits. Peak tissue concentrations were generally attained within 1 hour after dosing.

The ocular distribution study of radiolabelled drug in white rabbits indicated similar ocular distribution profile of ^{14}C-brimonidine tartrate for the **COMBIGAN®** (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution and brimonidine tartrate 0.2%, as well as similar ocular distribution profile of ^{3}H-timolol maleate for **COMBIGAN®** and timolol maleate 0.5%. Both timolol maleate and brimonidine tartrate are distributed to all parts of the eye with relatively high drug concentrations achieved in the cornea, conjunctiva, iris, ciliary body, and aqueous humor following administration with **COMBIGAN®**.

After a single ocular dose of ^{14}C-**COMBIGAN®** to albino rabbits, ^{14}C-brimonidine tartrate C_{max} in aqueous humor, iris, and ciliary body were 0.677, 1.99, and 1.81 µg-eq/g or mL, respectively. The corresponding ^{3}H-timolol maleate C_{max} in aqueous humor, iris, and ciliary body after a single dose of ^{3}H-**COMBIGAN®** to albino rabbits was 2.51, 6.65, and 5.75 µg-eq/g or mL, respectively. ^{14}C-brimonidine tartrate C_{max} in aqueous humor, iris, and ciliary body were 0.505, 1.30, and 1.21 µg-eq/g or mL, respectively, upon application of a single ocular dose of ^{14}C-brimonidine tartrate 0.2% solution (ALPHAGAN®). ^{3}H-timolol maleate C_{max} in aqueous humor, iris, and ciliary body were 1.64, 4.26, and 2.92 µg-eq/g or mL, respectively, after a single ocular dose of ^{3}H-timolol maleate 0.5% solution to albino rabbits.

In a 6-month toxicokinetics study in white rabbits, mean plasma timolol maleate C_{max} values after 25 weeks of TID dosing in one eye with **COMBIGAN®** and timolol maleate 0.5% treatment were 5.86 ng/mL and 10.4 ng/mL, respectively. The mean plasma brimonidine tartrate C_{max} values after 25 weeks of TID dosing in one eye with **COMBIGAN®** and brimonidine tartrate 0.2% were 1.39 ng/mL and 2.1 ng/mL, respectively.

Clinical Pharmacology

Pharmacodynamics
Elevated IOP presents a major risk factor in glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Fluctuation in IOP is related to the progression of glaucoma, with each 1 mm increase in IOP fluctuation raising the odds of progression in visual field loss by up to30%. Timolol maleate ophthalmic solution 0.5%, a non-selective beta-blocker lowers IOP by decreasing aqueous humor production. Brimonidine tartrate ophthalmic solution 0.2%, a selective and potent alpha-2 adrenoceptor agonist, reduces IOP through reduction of aqueous humor production and an increase in nonpressure-dependent uveoscleral outflow. **COMBIGAN®** is a combination product containing brimonidine tartrate 0.2% and timolol 0.5% as timolol maleate.

Pharmacokinetics
Plasma brimonidine tartrate and timolol maleate concentrations were determined in 16 healthy subjects dosed with **COMBIGAN®**, ALPHAGAN® (brimonidine tartrate) ophthalmic solution 0.2%, or TIMOPTIC® (timolol maleate) ophthalmic solution USP 0.5%, each BID for seven days in a three-period, complete crossover study. There were no statistically significant differences in brimonidine tartrate or timolol maleate AUC between **COMBIGAN®** and the respective monotherapy treatments. Mean plasma brimonidine tartrate C_{max} values from the **COMBIGAN®** and ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% groups were 0.0327 ± 0.0150 (N = 15) and 0.0347 ± 0.0226 ng/mL (N = 16), respectively, indicating no apparent difference. Mean plasma timolol maleate C_{max} values from the **COMBIGAN®** and TIMOPTIC® (timolol maleate ophthalmic solution) USP 0.5% treatment groups were 0.406 ± 0.216 (N = 15) and 0.507 ± 0.269 ng/mL (N = 14), respectively. Although the C_{max} of timolol maleate was approximately 20% lower in the **COMBIGAN®** treatment, the difference was not statistically significant (p=0.088).

Therapeutic drug monitoring was conduced in the two Phase 3 trials. Brimonidine tartrate and timolol maleate plasma concentrations from the **COMBIGAN®** BID group were 15-49% lower than their respective monotherapy values. In the case of brimonidine tartrate, the difference appears to be due to BID dosing for **COMBIGAN®** and TID dosing for ALPHAGAN®.

The lower timolol maleate plasma concentrations seen with **COMBIGAN®**, as compared to timolol maleate 0.5%, appear to be related to a slower absorption of timolol maleate, which may be due to a difference in the benzalkonium concentrations rather than a drug-drug (brimonidine tartrate-timolol maleate) interaction.

These results on systemic absorption of topical drug from **COMBIGAN®** versus monotherapy treatments are consistent with the more favourable safety profile demonstrated by the **COMBIGAN®** treatment, as compared to ALPHAGAN® TID and timolol maleate BID.

TOXICOLOGY

Acute Toxicity

The acute median lethal dose (LD_{50}) or minimum lethal dose (MLD) values of brimonidine tartrate were evaluated in mice, rats, rabbits, and dogs by oral and intravenous (i.v.) administration. The LD_{50} or MLD values for each study are listed below:

Species	Route	LD_{50} (mg/kg)*	MLD (mg/kg)*
Mouse	Oral i.v.*	50 50	>8** Not performed
Rat	oral i.v.	100 100-150	>8** Not performed
Rabbit	oral i.v.	Not performed Not performed	>6 20-50
Dog	oral i.v.	Not performed Not performed	0.5 0.05

* The doses are expressed as the base except in the mouse and rat MLD data, where they are expressed as brimonidine tartrate.

** The data from additional single dose oral studies of 0.2% and 0.5% solutions of brimonidine tartrate in mice and rats showed that the oral MLD is greater than 10 mg/kg.

The most frequently observed clinical signs in the acute/single dose toxicity studies were primarily due to the exaggerated pharmacological hypotensive effect of the compound. These signs included: sedation, ataxia, prostration, ptosis, reduced/loss of blink reflex, opacification of the cornea, hypotension, bradycardia, hypothermia, respiratory depression, respiratory arrest and circulatory collapse. The ocular changes were seen only after doses at or above the minimum lethal dose.

The oral LD_{50} of timolol maleate is 1190 mg/kg (3570 mg/m^2) in female mice and 900 mg/kg (5310 mg/m^2) in female rats.

Signs of toxicity including lacrimation, ataxia, tremors and bradypnea occurred immediately after intravenous administration and from 10 to 30 minutes following oral, intraperitoneal or subcutaneous administration. Clonic convulsions typically preceded death.

Long-term Toxicity

COMBIGAN® (brimonidine tartrate 0.2%/timolol maleate as timolol 0.5%) ophthalmic solution containing 50 ppm benzalkonium chloride was administered to New Zealand White rabbits as 1 drop in 1 eye 3 times daily for 6 months. Brimonidine tartrate 0.2% (alone), timolol maleate 0.5% (alone), and the vehicle for **COMBIGAN®** were used as comparators. All formulations were well tolerated. No ocular irritation and no pathological findings were observed in ocular or systemic tissue. Transient, slight ocular discomfort was noted for all formulations, including the vehicle. Slight, transient (<3 hrs) sedation was noted in rabbits treated with **COMBIGAN®** or brimonidine tartrate (alone). This effect is considered an exaggerated pharmacological effect of alpha-2-adrenergic receptor activation. Plasma C_{max} and AUC daily exposure values, respectively, for brimonidine tartrate (43 and 14 times) or timolol maleate (15 and 4.5 times)

were increased in the rabbit study above the similar values measured in humans treated with 1 drop of **COMBIGAN®** in both eyes 2 times per day.

Carcinogenicity
In studies with brimonidine tartrate, there was no compound-related oncogenic effect observed in either mice or rats.

The maximal brimonidine tartrate plasma concentrations after oral administration of 2.5 mg base/kg/day to mice for 21 months correspond to approximately 150 times the human systemic exposure to **COMBIGAN®** instilled in both eyes (one drop) twice daily. After two years of oral administration at 1.0 mg base/kg/day to rats, plasma C_{max} concentrations were approximately 210 times greater than those seen in humans receiving one drop of **COMBIGAN®** in both eyes BID. There were no observable tumorigenic effects seen in mice or rats dosed at 2.5 mg base/kg/day or 1.0 mg base/kg/day, (approximately 150 times and 210 times the recommended human ocular dose), respectively.

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 human daily dose of **COMBIGAN®**). Similar differences were not observed in rats administered oral doses equivalent to approximately 8,300 times the maximum recommended human ophthalmic dose.

In a lifetime oral study 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 human daily dose of **COMBIGAN®**), but not at 5 or 50 mg/kg/day (approximately 420 to 4,200, respectively, times the human daily dose of **COMBIGAN®**). 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 maleate 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.

Mutagenicity
Brimonidine tartrate was not mutagenic or cytogenetic in a series of *in vitro* and *in vivo* studies including the Ames/Salmonella mutagenicity assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenetic assay, host-mediated assay and dominant lethal assay in mice.

Timolol maleate was negative for 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 μg/mL). In the Ames assays the highest concentrations of timolol maleate, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants with tester strain TA 100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, and the ratio of test to control revertants was less than 2. A ratio of 2 is usually considered the criterion for a positive response with strain TA100.

Reproduction and Teratology
Reproductive toxicology studies conducted with brimonidine tartrate in rats and rabbits showed that brimonidine tartrate had no adverse effects on fertility and general reproductive performance, and showed no evidence of embryolethality or teratogenicity at the dosages administered.

The mean maximal plasma brimonidine tartrate concentrations measured during the rat teratogenicity study (1.65 mg base/kg/day, orally) were approximately 600 times the maximum human systemic exposure to **COMBIGAN®** instilled in each eye (one drop) twice daily. Mean maximal plasma brimonidine concentrations in the rabbit teratogenicity study (3.33 mg base/kg/day, orally) were approximately 43 times greater than plasma concentrations seen in humans receiving one drop of **COMBIGAN®** in each eye BID.

There were no treatment-related reproductive and teratological effects observed in the F1 rat pup group, although a reduction in body weight was observed at a dose level of 1.65 mg base/kg/day, after 14 days. Dose related reduction in body weight gains were observed in rat dams at dose levels of 0.66 and 1.65 mg base/kg/day after 15 days.

Body weight loss, reduced food consumption, and spontaneous abortions occurred in two of eight rabbits at the 3.3 mg base/kg/day level (gestation day 21 or 23), and may have been the result of the exaggerated pharmacological effects observed at this level. No abortions occurred at the 0.165 or 0.66 mg base/kg/day level. Maternal necropsy was generally unremarkable. There was no evidence of treatment-related embryotoxicity, fetal toxicity, or teratogenicity at dosage levels up to 3.3 mg base/kg/day (approximately 825 times the recommended daily human ocular dose of **COMBIGAN®**). In another study involving 20 rabbit dams, dosed orally up to 2.64 mg base/kg/day, no adverse effects were observed other than a decrease in weight gain during the dosing period, and no treatment related embryolethal or teratogenic effects were observed.

Reproduction and fertility studies in rats with timolol maleate showed no adverse effect on male or female fertility at doses up to 4,200 times the maximum recommended human ocular dose of **COMBIGAN®**.

Teratogenicity studies with timolol maleate in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (4,200 times the daily human dose of **COMBIGAN®**) 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 1000 mg/kg/day (83,000 times the daily human dose of **COMBIGAN®**) were maternotoxic in mice and resulted

in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 8,300 times higher than the maximum recommended human ophthalmic dose of **COMBIGAN®**, in this case without apparent maternotoxicity.

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PART III: CONSUMER INFORMATION

[Pr]COMBIGAN®
Combination of brimonidine tartrate 0.2% and timolol 0.5% as timolol maleate

This leaflet is part III of a three-part "Product Monograph" published when COMBIGAN® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COMBIGAN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
COMBIGAN® is used for:

- Reducing pressure in the eye (intraocular pressure, or IOP). This high pressure can lead to a disease called glaucoma. If the high pressure is not reduced, it could eventually damage your sight.

What it does:
The eye contains a clear, watery liquid. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up. **COMBIGAN®** is a preserved eye drop solution that reduces the amount of fluid flowing into the eye and increases the amount of fluid flowing out of the eye.

Remember: This medication is prescribed for the particular condition you have. Do not give this medication to other persons or use it for any other condition.

When it should not be used:
Do not use **COMBIGAN®** if you:

- Are allergic to any of its components (See what the nonmedicinal ingredients are.)
- Have asthma or have ever had asthma
- Have chronic obstructive lung disease (COPD)
- Have certain heart diseases or conditions
- Have diabetes or are subject to low blood sugar levels without apparent cause
- Are receiving monoamine oxidase (MAO) inhibitor therapy
- Are breast-feeding or pregnant

It should also not be used in children under the age of 2 years.

What the medicinal ingredients are:
This product contains two medicinal ingredients. It is a combination of brimonidine tartrate 0.2% and timolol 0.5% as timolol maleate

What the important nonmedicinal ingredients are:
Benzalkonium chloride

Other nonmedicinal ingredients in the product include: sodium phosphate, monobasic monohydrate; sodium phosphate, dibasic heptahydrate; purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

What dosage forms it comes in:
COMBIGAN® is supplied in white, opaque plastic dropper bottles containing: 2.5 mL, and 10 mL.

WARNINGS AND PRECAUTIONS

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.

BEFORE you use COMBIGAN® talk to your doctor or pharmacist if:

- **You have or have had kidney or liver problems in the past.**
- **You have had thyroid problems in the past.**
- **You have had eye problems in the past, such as choroidal detachment.**
- **You have had problems or develop problems with blood flow to the brain.**
- **You have any medical problems now or have had any in the past, especially asthma and other lung problems, heart problems or heart disease.**
- **You have diabetes or are subject to low blood sugar levels without apparent cause.**
- **You have myasthenia gravis or myasthenic symptoms (e.g., general weakness, double vision, droopy eyelid).**
- **You are experiencing depression.**
- **You are pregnant or intend to become pregnant.**
- **You are breast-feeding or intend to breast-feed. Timolol has been detected in human breast milk. Discuss with your doctor.**
- **You are planning to have major surgery. If you will be administered an anesthetic, inform your anesthetist before surgery that you are taking COMBIGAN®.**
- **If you have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection). Immediately seek your physician's advice concerning the continued use of the present multidose container.**
- **You have any allergies to this drug, or to similar drugs (ask your doctor) or to COMBIGAN®'s ingredients or components of its container**
- **You are taking or intend to take other prescription or non-prescription drugs. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease.**

- **You wear contact lenses. The preservative in COMBIGAN® (benzalkonium chloride) may be absorbed by and change the color of soft (hydrophilic) contact lenses. Lenses should be removed prior to application of COMBIGAN® and kept out for 15 minutes after use.**
- **You drive or operate heavy equipment. This medication may potentially cause fatigue and/or drowsiness in some patients. This medication may also cause blurred vision or visual disturbance upon instillation. You should wait until these symptoms have cleared before driving or using machinery.**

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with COMBIGAN® include:

Heart or blood pressure medications, such as beta-blockers, calcium channel blockers, catecholamine depleting drugs such as reserpine, epinephrine, tricyclic depressants, quinidine, clonidine, alcohol, other central nervous system depressants, antiarrhythmics (e.g. amiodarone), guanethidine and digitalis glycosides.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
The usual dose is one drop in the affected eye(s) in the morning and in the evening.

If you are using COMBIGAN® with another eyedrop, the drops should be instilled at least 10 minutes apart.
Do not allow the tip of the dropper to touch your eye or any of the areas right around your eye, to avoid eye injury and contamination of eye drops. Touching other areas may contaminate the solution, and you may develop a serious eye infection.

Overdose:

In case of drug overdose, contact your healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

Symptoms of overdose include dizziness, headache, shortness of breath, low blood pressure, slow heart beat, difficulty breathing, and cardiac arrest. These symptoms may occur if the overdose is to the eyes, or if the contents of the bottle are accidentally swallowed.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some common side effects which may occur include dry mouth, burning/stinging eye(s), itchy eye(s), dry eyes, eye pain, swollen/inflamed/bloodshot eyes, blurred vision, and headache. If these persist or cause you concern, consult your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Severe allergic reaction and symptoms, such as swelling of the mouth and throat, difficulty in breathing, hives, severe itching and rash			✓
	Slow heartbeat		✓	
	Heart effects such as irregular heartbeat, heart block, and low blood pressure		✓	
	Worsening of asthma, difficulty breathing			✓
	Low blood sugar levels			✓

This is not a complete list of side effects. For any unexpected effects while taking COMBIGAN®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 - 25°C). Protect from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Allergan Inc. at: 1-800-668-6424

This leaflet was prepared by Allergan Inc.

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