COMBIGAN®

QUALITATIVE AND QUANTITATIVE COMPOSITION

brimonidine tartrate 0.2% w/v
timolol (as maleate) 0.5% w/v

Excipient(s) with known effect:
Contains benzalkonium chloride 0.05 mg/mL
Contains phosphates 10.58 mg/mL

For the full list of excipients, see section 11.

1 PHARMACEUTICAL FORM

Eye drops, solution

2 INDICATIONS AND USAGE

Combigan is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

3 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) twice daily approximately 12 hours apart.

If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

4 CONTRAINDICATIONS

4.1 Reactive Airway Disease Including Asthma, COPD

COMBIGAN is contraindicated in patients with reactive airway disease including bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease *[see Warnings and Precautions (5.1, 5.3)]*.

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock

COMBIGAN is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure *[see Warnings and Precautions (5.2)]*; cardiogenic shock.

4.3 Neonates and Infants (Pediatric Patients Younger than 2 Years Old)

COMBIGAN is contraindicated in neonates and infants (pediatric patients younger than 2 years old) *[see Use in Specific Populations (8.4)]*.

4.4 Hypersensitivity Reactions

Local hypersensitivity reactions have occurred following the use of different components of **COMBIGAN. COMBIGAN** is contraindicated in patients who have exhibited a hypersensitivity reaction to the active substances or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Severe Respiratory or Cardiac Reactions

COMBIGAN contains timolol maleate; and although administered topically can be absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions 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 (4.1)]*. Additionally, ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension.

5.2 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 *[see Contraindications (4.2)]*.

5.3 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 (4.1)])* should, in general, not receive beta-blocking agents, including **COMBIGAN**.

5.4 Potentiation of Vascular Insufficiency

COMBIGAN may potentiate syndromes associated with vascular insufficiency. **COMBIGAN** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

5.5 Increased Reactivity to Allergens

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.6 Potentiation of Muscle Weakness

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

5.7 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus

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

5.8 Masking of Thyrotoxicosis

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

5.9 Ocular Hypersensitivity

Ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solutions 0.2%, with some reported to be associated with an increase in intraocular pressure *[see Contraindications (4.4)]*.

5.10 Contamination of Topical Ophthalmic Products After Use

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. Do not touch the tip of the dispensing container to the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

5.11 Impairment of Beta-adrenergically Mediated Reflexes During Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

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

5.12 Benzalkonium Chloride

The preservative in Combigan, benzalkonium chloride, may cause eye irritation, symptoms of dry eyes, and may affect the tear film and corneal surface with prolonged use. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

Combigan should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

5.13 Phosphates buffer

Combigan contains phosphates, which may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

5.14 Effects on ability to drive and use machines

As with other similar medications, COMBIGAN may cause fatigue and/or drowsiness in some patients. Patients who engage in activities such as driving and operating machinery should be cautioned of the potential for a decrease in mental alertness. COMBIGAN may also cause blurred vision or visual disturbance in some patients. The patient should wait until these symptoms have cleared before driving or using machinery.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Contraindications (4.4)]*
- Potential for Severe Respiratory or Cardiac Reactions *[see Warnings and Precautions (5.1)]*
- Cardiac Failure *[see Warnings and Precautions (5.2)]*
- Potentiation of Vascular Insufficiency *[see Warnings and Precautions (5.4)]*
- Increased Reactivity to Allergens *[see Warnings and Precautions (5.5)]*
- Potentiation of Muscle Weakness *[see Warnings and Precautions (5.6)]*
- Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.7)]*
- Masking of Thyrotoxicosis *[see Warnings and Precautions (5.8)]*
- Ocular Hypersensitivity *[see Warnings and Precautions (5.9)]*

- Contamination of Topical Ophthalmic Products after Use *[see Warnings and Precautions (5.10)]*
- Impairment of Beta-adrenergically Mediated Reflexes During Surgery *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

COMBIGAN

In clinical trials of 12 months duration with **COMBIGAN**, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The following adverse reactions were reported in 1% to 5% of patients: asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

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

Brimonidine Tartrate (0.1%-0.2%)

Abnormal taste, allergic reaction, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival blanching, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), hordeolum, insomnia, keratitis, lid crusting, lid disorder, muscular pain, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, superficial punctate keratopathy, tearing, upper respiratory symptoms, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity

Timolol (Ocular Administration)

- *Body as a whole*: chest pain
- *Cardiovascular*: Arrhythmia, bradycardia, cardiac arrest, cardiac failure, cerebral ischemia, cerebral vascular accident, claudication, cold hands and feet, edema, heart block, palpitation, pulmonary edema, Raynaud's phenomenon, syncope, and worsening of angina pectoris
- *Digestive*: anorexia, diarrhea, nausea
- *Immunologic*: Systemic lupus erythematosus
- *Nervous System/Psychiatric*: Increase in signs and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss
- *Skin*: Alopecia, psoriasiform rash or exacerbation of psoriasis
- *Hypersensitivity*: Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and generalized and localized rash; *Respiratory*: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease) *[see Contraindications (4.1)]*, dyspnea, nasal congestion, respiratory failure, upper respiratory infections
- *Endocrine*: Masked symptoms of hypoglycemia in diabetes patients *[see Warnings and Precautions (5.7)]*
- *Special Senses*: diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudopemphigoid, ptosis, refractive changes, tinnitus
- *Urogenital*: Decreased libido, impotence, Peyronie's disease, retroperitoneal fibrosis.

6.2 Postmarketing Experience

The following reactions have been identified during postapproval use of brimonidine tartrate ophthalmic solutions, timolol ophthalmic solutions, or both in combination, in clinical practice. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Bradycardia, eyelid erythema extending to the cheek or forehead, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, rash, and vasodilation), syncope, and tachycardia.
- Apnea, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications (4.3) and Use in Specific Populations (8.4)]*.

Oral Timolol/Oral Beta-blockers

The following additional adverse reactions have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate:

- *Allergic*: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress
- *Body as a whole*: Decreased exercise tolerance, extremity pain, weight loss
- *Cardiovascular*: Vasodilatation, worsening of arterial insufficiency
- *Digestive*: Gastrointestinal pain, hepatomegaly, ischemic colitis, mesenteric arterial thrombosis, vomiting
- *Hematologic*: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Endocrine*: Hyperglycemia, hypoglycemia; *Skin*: Increased pigmentation, pruritus, skin irritation, sweating
- *Musculoskeletal*: Arthralgia
- *Nervous System/Psychiatric*: An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometrics, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly clouded sensorium, vertigo
- *Respiratory*: Bronchial obstruction, rales
- *Urogenital*: Urination difficulties

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Antihypertensives /Cardiac Glycosides

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

7.2 Beta-adrenergic Blocking Agents

Patients who are receiving a beta-adrenergic blocking agent either orally or intravenously 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.

7.3 Calcium Antagonists

Caution should be used in the co-administration 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, co-administration should be avoided.

7.4 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.

7.5 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.

7.6 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.

7.7 CYP2D6 Inhibitors

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

7.8 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.

Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

7.9 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side effect such as hypotension. Caution, however, is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies with COMBIGAN in pregnant women. Limited available data from postmarketing safety reports and published literature reviews with COMBIGAN use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes (see Data).

In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.
Oral administration of brimonidine tartrate or timolol maleate to pregnant rats and rabbits during organogenesis at dose exposures 580 and 37 times the recommended human ophthalmic dose (RHOD) resulted in no adverse developmental effects (see Data).

Oral administration of timolol maleate to mice, rats, and rabbits during organogenesis at dose exposures up to 4,200 times the RHOD resulted in no evidence of fetal malformations (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Data
Human Data
Limited available data from postmarketing safety reports and published literature with topical use of brimonidine ophthalmic solution in pregnant women are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes including miscarriage, stillbirth, congenital anomaly, and events experienced by the breastfed infant.
Animal Data

Embryofetal development studies were conducted with oral administration of brimonidine tartrate during organogenesis in rats (gestation days 6 to 15) and rabbits (gestation days 6 to 18). No adverse developmental effects were observed in rats up to 2.5 mg/kg/day and rabbits up to 5 mg/kg/day. These doses represent exposures 580 and 37 times higher, respectively, than the recommended human ophthalmic dose (RHOD) of **COMBIGAN** at 1 drop in both eyes twice daily.

Orally administered brimonidine crossed the placenta in pregnant rats and entered the fetal circulation to a limited extent.

Embryofetal development studies conducted with timolol during organogenesis in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human ophthalmic dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)] demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (83,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 8,300 times the MRHOD without apparent maternotoxicity.

8.2 Lactation

Risk Summary
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. In animal studies, brimonidine tartrate has been shown to be excreted in breast milk.

Because of the potential for serious adverse reactions in the breastfed infant, including central nervous system depression and apnea, COMBIGAN is not recommended for use during lactation.

Data
Animal Data
After a single oral dose of ^{14}C-labeled brimonidine tartrate to lactating rats, brimonidine tartrate and trace metabolites were detected in milk after 30 minutes. There was 30% higher milk concentration compared to maternal plasma concentration 30 minutes after dosing and a 10-fold higher milk concentration compared to maternal plasma concentration 8 hours after dosing. No radiolabeled brimonidine tartrate or metabolites were detectable in milk 24 hours after dosing.

8.4 Pediatric Use
COMBIGAN is contraindicated in pediatric patients younger than 2 years old *[see Contraindications (4.3)]*. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of 2 years.

The safety and effectiveness of **COMBIGAN** have been established in pediatric patients aged 2 years and older. Use of **COMBIGAN** for this indication is supported by evidence from adequate and well-controlled studies of **COMBIGAN** in adults with additional data from a study of the concomitant use of brimonidine tartrate ophthalmic solution 0.2% and timolol maleate ophthalmic solution in pediatric glaucoma patients (ages 2 to 7 years).

In this well-controlled clinical study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50% to 83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

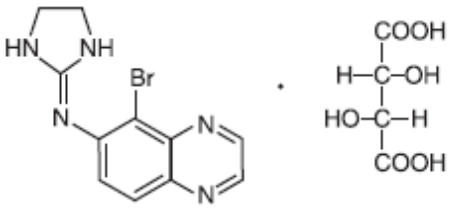
8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

10 OVERDOSAGE
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. With the exception of hypotension, very limited information exists on accidental ingestion of brimonidine in adults. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine ophthalmic solutions as part of medical treatment of congenital glaucoma or by accidental oral ingestion *[see Use in Specific Populations (8.4)]*. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

11 DESCRIPTION
COMBIGAN (brimonidine tartrate and timolol maleate; eye drops, solution) 0.2%/0.5%, sterile, contains brimonidine tartrate, a relatively selective alpha-2 adrenergic receptor agonist, and timolol maleate, a non-selective beta-adrenergic receptor inhibitor (topical intraocular pressure lowering agent) for topical ophthalmic use.

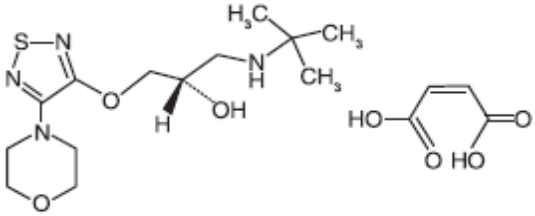
The structural formulae are:

Brimonidine tartrate:



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

Timolol maleate:



(-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1) (salt); MW= 432.50 as the maleate salt

In solution, **COMBIGAN** has a clear, greenish-yellow to light greenish-yellow color. It has an osmolality of 260-330 mOsmol/kg and a pH during its shelf life of 6.5-7.3.

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

COMBIGAN contains the active ingredients brimonidine tartrate 0.2% and timolol (as maleate) 0.5% (6.8 mg/mL timolol maleate) with the inactive ingredients: sodium phosphate dibasic, heptahydrate; sodium phosphate monobasic, monohydrate; benzalkonium chloride 0.005%; hydrochloric acid and/or sodium hydroxide to adjust pH; and purified water.

12 CLINICAL PHARMACOLOGY

12.1 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 relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor. Both brimonidine and timolol have a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing for brimonidine and one to two hours for timolol.

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

Timolol maleate is a $beta_1$ and $beta_2$ adrenergic receptor inhibitor that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

12.3 Pharmacokinetics

Absorption

Systemic absorption of brimonidine and timolol was assessed in healthy volunteers and patients following topical dosing with **COMBIGAN**. Normal volunteers dosed with one drop of **COMBIGAN** twice daily in both eyes for seven days showed peak plasma brimonidine and timolol concentrations of 30 pg/mL and 400 pg/mL, respectively. Plasma concentrations of brimonidine peaked at 1 to 4 hours after ocular dosing. Peak plasma concentrations of timolol occurred approximately 1 to 3 hours post-dose.

In a crossover study of **COMBIGAN**, brimonidine tartrate 0.2%, and timolol 0.5% administered twice daily for 7 days in healthy volunteers, the mean brimonidine area-under-the-plasma-concentration-time curve (AUC) for **COMBIGAN** was 128 ± 61 pg•hr/mL versus 141 ± 106 pg•hr/mL for the respective monotherapy treatments; mean C_{max} values of brimonidine were comparable following **COMBIGAN** treatment versus monotherapy (32.7 ± 15 pg/mL versus 34.7 ± 22.6 pg/mL, respectively). Mean timolol AUC for **COMBIGAN** was similar to that of the respective monotherapy treatment (2919 ± 1679 pg•hr/mL versus 2909 ± 1231 pg•hr/mL, respectively); mean C_{max} of timolol was approximately 20% lower following **COMBIGAN** treatment versus monotherapy.

In a parallel study in patients dosed twice daily with **COMBIGAN**, twice daily with timolol 0.5%, or three times daily with brimonidine tartrate 0.2%, one-hour post dose plasma concentrations of timolol and brimonidine were approximately 30-40% lower with **COMBIGAN** than their respective monotherapy values. The lower plasma brimonidine concentrations with **COMBIGAN** appears to be due to twice-daily dosing for **COMBIGAN** versus three-times dosing with brimonidine tartrate 0.2%.

Distribution

The protein binding of timolol is approximately 60%. The protein binding of brimonidine is approximately 29%.

Elimination

Metabolism

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

Excretion

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

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the urine. Unchanged timolol and its metabolites are excreted by the kidney.

Special Populations

Patients with Renal Impairment

COMBIGAN has not been studied in patients with renal impairment.

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

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

Patients with Hepatic Impairment

COMBIGAN has not been studied in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

With brimonidine tartrate, no compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 210 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **COMBIGAN** into both eyes twice daily, the recommended daily human dose.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day [approximately 25,000 times the maximum recommended human ocular dose of 0.012 mg/kg/day on a mg/kg basis (MRHOD)]. Similar differences were not observed in

rats administered oral doses equivalent to approximately 8,300 times the daily dose of **COMBIGAN** in humans.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 42,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 420 to 4,200 times higher, respectively, than the MRHOD). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Mutagenesis
Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Impairment of Fertility
Reproduction and fertility studies in rats with timolol maleate and in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose of **COMBIGAN**.

14 CLINICAL STUDIES

Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of **COMBIGAN** administered twice a day (BID) to individually-administered brimonidine tartrate ophthalmic solution, 0.2% administered three times per day (TID) and timolol maleate ophthalmic solution, 0.5% BID in patients with glaucoma or ocular hypertension. **COMBIGAN** BID provided an additional 1 to 3 mm Hg decrease in IOP over brimonidine treatment TID and an additional 1 to 2 mm Hg decrease over timolol treatment BID during the first 7 hours post dosing. However, the IOP-lowering of **COMBIGAN** BID

was less (approximately 1-2 mm Hg) than that seen with the concomitant administration of 0.5% timolol BID and 0.2% brimonidine tartrate TID. **COMBIGAN** administered BID had a favorable safety profile versus concurrently administered brimonidine TID and timolol BID in the self-reported level of severity of sleepiness for patients over age 40.

16 HOW SUPPLIED/ STORAGE AND HANDLING

COMBIGAN is supplied sterile, in white opaque plastic LDPE bottles and tips, with blue high impact polystyrene (HIPS) caps as follows:

5 mL in 10 mL bottle
10 mL in 10 mL bottle

Storage: Store below 25ºC. Protect from light.
After first opening, use within 28 days. Replace the cap after use.
The expiry date of the product is indicated on the packaging materials.

17 MANUFACTURER

Allergan Inc., USA, 2525 Dupont Drive, Irvine, California, USA.

18 REGISTRATION HOLDER

AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.

19 MARKETING AUTHORIZATION NUMBER

137-56-31401-00

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