Indication: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is approved for reducing elevated intraocular pressure (IOP) in patients with glaucoma who require additional or adjunctive IOP-lowering therapy. COMBIGAN® lowers IOP slightly less than both brimonidine tartrate taken 3 times a day and timolol maleate taken 2 times a day.
All about high eye pressure and COMBIGAN®

This brochure will help you learn more about glaucoma and how COMBIGAN® may help to reduce high eye pressure, also known as intraocular pressure (IOP), for people who have open-angle glaucoma or ocular hypertension.

We hope that you will find this information useful. If you have any questions, please discuss them with your physician.

IMPORTANT SAFETY INFORMATION

Contraindications: COMBIGAN® ophthalmic solution should not be used by patients who have, or ever had, bronchial asthma, chronic bronchitis, emphysema, slow heartbeat, impaired conduction of the heart, heart failure, or impaired pumping of the heart, or by patients with hypersensitivity to any ingredient of this product.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions: Severe respiratory reactions including death due to difficulty breathing have been reported in patients with asthma. Stimulation of the nervous system may be essential in individuals with diminished heart pumping ability. In patients without a history of cardiac failure, continued use of beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.
Why is eye pressure important?

A number of factors may contribute to glaucoma, but high pressure inside the eye, also known as high intraocular pressure (IOP), plays a very important role.

- Your eyes contain fluid that keeps them nourished and healthy
- Normally, this fluid flows within the eye and drains freely
- In people who have open-angle glaucoma, the fluid does not drain properly
- The buildup of fluid causes pressure inside the eye to rise
- If the pressure remains high for a long time, it can slowly cause damage to the optic nerve, potentially leading to glaucoma-related vision loss
- The higher the eye pressure becomes, the greater the risk for optic nerve damage and vision loss

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued): Patients with mild or moderate chronic bronchitis, emphysema, or asthma should not take COMBIGAN® ophthalmic solution. COMBIGAN® may worsen symptoms associated with poor circulation. COMBIGAN® patients who have allergies may experience stronger allergy symptoms than they would without COMBIGAN® ophthalmic solution. Patients may experience muscle weakness or fatigue. COMBIGAN® may mask hypoglycemic symptoms in patients with diabetes mellitus.
**What is COMBIGAN®?**

You are most likely one of the 2.2 million people in the United States who have open-angle glaucoma.² Twice-daily COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is a medication proven to effectively lower IOP for patients who require additional or adjunctive IOP-lowering therapy. COMBIGAN® lowers IOP slightly less than both brimonidine tartrate taken 3 times a day and timolol maleate taken 2 times a day.¹

COMBIGAN® combines 2 treatments (active ingredients)—brimonidine and timolol—in 1 bottle. Instead of prescribing these 2 medications separately, your physician has chosen to prescribe COMBIGAN®.

**Why did my physician prescribe COMBIGAN® for me?**

COMBIGAN® is specifically approved to lower high or elevated pressure in the eyes of people with primary open-angle glaucoma or ocular hypertension (both conditions involve elevated pressure in the eye) who require additional or adjunctive IOP-lowering therapy.¹

**IMPORTANT SAFETY INFORMATION (continued)**

**Adverse reactions:** The most common adverse reactions occurring in approximately 5% to 15% of patients included allergic inflammation of the eye, abnormally large lymph follicles in the mucous membrane lining the inner surface of the eyelid and the exposed surface of the eyeball (also called the conjunctiva), eye redness, severe itching of the eye, and burning and stinging of the eyes.
How does COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% work?

COMBIGAN® is believed to work in 2 different ways¹:
1. It decreases the amount of fluid **produced in the eye**
2. It increases fluid **that flows out of the eye**

Is COMBIGAN® the same thing as taking brimonidine and timolol (the 2 treatments in COMBIGAN®), separately?

No, COMBIGAN® is a specially formulated combination of these 2 treatments for reducing elevated intraocular pressure (IOP) in patients with glaucoma who require additional or adjunctive IOP-lowering therapy. COMBIGAN® lowers IOP slightly less than both brimonidine tartrate taken 3 times a day and timolol maleate taken 2 times a day.

In a clinical study of 385 patients taking COMBIGAN®, 5.2% of them experienced allergic conjunctivitis.²

**IMPORTANT SAFETY INFORMATION (continued)**

**Drug interactions:** Blood pressure drugs and drugs that are used to stimulate the heart in cases of heart failure (also called cardiac glycosides) may lower blood pressure. Using COMBIGAN® ophthalmic solution together with beta-blocker drugs may interrupt beta-receptor activity (beta-blockade) within the body.
How much does COMBIGAN® cost?

The cost of COMBIGAN® will be determined by your health plan.


Be sure to ask your eye care professional about available offers and coupons.

How will I know if COMBIGAN® is working?

Only your physician can test how well this medicine is working. It is important to follow up and make appointments to have your eye pressure checked as your physician instructs.

IMPORTANT SAFETY INFORMATION (continued)

Drug interactions (continued):

Oral or intravenous calcium channel blockers that prevent calcium from entering the cells of the heart and blood vessels (calcium antagonists) may cause disturbances in the passage of blood through the heart, and/or abnormally low blood pressure. Drugs that significantly decrease fluids of the adrenal gland may produce low blood pressure and/or a noticeably slow heartbeat rate below 60 beats per minute. Using COMBIGAN® with central nervous system depressants may result in an increased effect. Using COMBIGAN® with digitalis, a cardiac stimulant, may have added effects in prolonging the time it takes for blood to pass through the heart. CYP2D6 inhibitors may enhance the effect of beta-blockade within the body.

Indication: COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is approved for reducing elevated intraocular pressure (IOP) in patients with glaucoma who require additional or adjunctive IOP-lowering therapy. COMBIGAN® lowers IOP slightly less than both brimonidine tartrate taken 3 times a day and timolol maleate taken 2 times a day.
How often should I take COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%?

It is recommended that patients put 1 drop of COMBIGAN® in the affected eye(s) twice daily, 12 hours apart.1

Follow these 5 steps:

1. Wash your hands. Tilt your head back and look at the ceiling.*

2. Using your index finger, gently pull down your lower eyelid to form a pocket.

3. Gently squeeze 1 drop into the pocket. Do not let the bottle tip touch your eye, your fingers, or anything else.

What to do if you wear contact lenses

COMBIGAN® ophthalmic solution contains a preservative that may be absorbed by contact lenses. Contacts should be removed before you use COMBIGAN®.

What to do if you take more than 1 type of eyedrop

If you take other eyedrops besides COMBIGAN® ophthalmic solution, they should be administered at least 5 minutes apart.

4. Gently close your eyes and lightly press on the inside corners of your eyes.

5. Then carefully blot away any excess liquid that may be on your skin.

*If you wear contact lenses, remove them first, then wait 15 minutes after using COMBIGAN® ophthalmic solution before you put them back into your eyes.1

IMPORTANT SAFETY INFORMATION

Contraindications: COMBIGAN® ophthalmic solution should not be used by patients who have, or ever had, bronchial asthma, chronic bronchitis, emphysema, slow heartbeat, impaired conduction of the heart, heart failure, or impaired pumping of the heart, or by patients with hypersensitivity to any ingredient of this product.
How to handle your COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% bottle

It is very important to handle your COMBIGAN® bottle carefully. Always wash your hands before putting the drops in your eyes. Don’t allow anything to touch the tip—not even your eyes or the areas around your eyes! Potentially harmful bacteria may enter the bottle and cause serious eye infections. If you think your COMBIGAN® bottle has become contaminated, contact your eye care professional.

Why is it important to take COMBIGAN® every day?

Even if you feel fine, it’s important to continue using your COMBIGAN® eyedrops every day as your doctor prescribed. Do not skip or stop treatment before speaking with your doctor. Using COMBIGAN® may help lower your high eye pressure. Make it part of your daily routine.

Follow some helpful tips to remember to take your eyedrops:

• Associate using your eyedrops with other daily routines you’ve established for yourself, such as brushing your teeth
• Set a daily clock or watch alarm that can remind you to use your eyedrops
• Ask a friend or family member to remind you when it’s time to use your eyedrops

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions: Severe respiratory reactions including death due to difficulty breathing have been reported in patients with asthma. Stimulation of the nervous system may be essential in individuals with diminished heart pumping ability. In patients without a history of cardiac failure, continued use of beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.
Open-angle glaucoma is a lifelong disease

Open-angle glaucoma is a lifelong disease, which means treatment is also lifelong. Remembering to take your eyedrops is easier if you make them another part of your daily routine. Committing to taking your IOP-lowering medication exactly as prescribed is the best way to help manage your type of glaucoma and to lower high eye pressure.

If anything interferes with your ability to take your medicine as prescribed—such as too many eyedrops to manage in your daily routine—be sure to talk to your eye care professional.

Will COMBIGAN® cure my type of glaucoma?

No. There is no cure for open-angle glaucoma. It is a chronic disease, but taking your eye medication as prescribed is one of the things you can do to help lower eye pressure.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued): Patients with mild or moderate chronic bronchitis, emphysema, or asthma should not take COMBIGAN® ophthalmic solution. COMBIGAN® may worsen symptoms associated with poor circulation. COMBIGAN® patients who have allergies may experience stronger allergy symptoms than they would without COMBIGAN® ophthalmic solution. Patients may experience muscle weakness or fatigue. COMBIGAN® may mask hypoglycemic symptoms in patients with diabetes mellitus. Certain clinical signs of hyperthyroidism may be masked, such as rapid heartbeat. Patients with overactive thyroid who withdraw too abruptly from COMBIGAN® may experience severe hyperthyroid symptoms.
You play the most important part in your treatment

The success of your therapy ultimately depends on you and your ongoing daily commitment to taking your medication as your doctor prescribed.

What should I expect with COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% therapy?

Large clinical studies have shown that COMBIGAN® is effective for reducing high eye pressure in patients with open-angle glaucoma and ocular hypertension. In 5% to 15% of patients (n = 385), the following adverse events were reported:

- Eye allergies and inflammation
- Redness of the eyes
- Itchiness or burning sensation in the eyes
- Stinging

COMBIGAN® eyedrops can be absorbed by your body. Contact your eye care professional right away if you experience any of the following potential serious side effects:

- Shortness of breath
- Visual changes
- Irregular heartbeat and/or slowing of your heart rate

COMBIGAN® ophthalmic solution may cause fatigue and/or drowsiness. If you drive or perform hazardous work, such as operating machinery, make sure you feel appropriately alert. These are not the only risks associated with COMBIGAN®. If you experience these or other side effects, you should immediately contact your eye doctor.

IMPORTANT SAFETY INFORMATION (continued)

Drug interactions: Blood pressure drugs and drugs that are used to stimulate the heart in cases of heart failure (also called cardiac glycosides) may lower blood pressure. Using COMBIGAN® ophthalmic solution together with beta-blocker drugs may interrupt beta-receptor activity (beta-blockade) within the body. Oral or intravenous calcium channel blockers that prevent calcium from entering the cells of the heart and blood vessels (calcium antagonists) may cause disturbances in the passage of blood through the heart, and/or abnormally low blood pressure. Drugs that significantly decrease fluids of the adrenal gland may produce low blood pressure and/or a noticeably slow heartbeat rate below 60 beats per minute.
Who should NOT use COMBIGAN®

COMBIGAN® should not be used if you are currently taking a type of antidepressant called an “MAO inhibitor” or if you have:

- Bronchial asthma or a history of bronchial asthma
- Severe lung problems
- Slow or irregular heartbeat or heart failure
- Allergies to any of the ingredients in COMBIGAN®

COMBIGAN® eyedrops can be absorbed by your body, which may be of concern if you have other medical conditions or are taking other drugs.

So tell your doctor about your other medications, especially:

- Heart or blood pressure medicines, such as beta-blockers and calcium channel blockers
- Sedatives
- Antidepressants

It is also very important to tell your doctor if you have:

- Diabetes
- Thyroid problems
- Liver or kidney disease
- Depression
- Eye injury or infection
- Upcoming surgery for your eyes or anywhere on your body

These risks are not the only risks associated with COMBIGAN®. If you experience these or other side effects, you should immediately contact your eye care professional.

IMPORTANT SAFETY INFORMATION (continued)

Drug interactions (continued): Using COMBIGAN® with central nervous system depressants may result in an increased effect. Using COMBIGAN® with digitalis, a cardiac stimulant, may have added effects in prolonging the time it takes for blood to pass through the heart. CYP2D6 inhibitors may enhance the effect of beta-blockade within the body. Tricyclic antidepressants may reduce the ability of clonidine to lower blood pressure. Monoamine oxidase inhibitors (a type of antidepressant drug) may result in low blood pressure.

Please see full prescribing information on the following pages

Not actual patients.
**COMBIGN®**
(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use COMBIGN® safely and effectively. See full prescribing information for COMBIGN®.

**COMBIGN®** (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%
Initial U.S. Approval: 2007

**INDICATIONS AND USAGE**

COMBIGN® is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of COMBIGN® dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution, 0.2% dosed three times per day. (1)

**DOSE AND ADMINISTRATION**

- One drop in the affected eye(s), twice daily approximately 12 hours apart. (2)

**DOSE FORMS AND STRENGTHS**

- Solution containing 2 mg/mL brimonidine tartrate and 5 mg/mL timolol. (3)

**CONTRAINDICATIONS**

- Bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease. (4, 5.1, 5.3)
- Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock. (4, 5.2)
- Hypersensitivity to any component of this product. (4)

**WARNINGS AND PRECAUTIONS**

- Potentiation of Respiratory Reactions Including Asthma (5.1)
- Cardiac Failure (5.2)
- Obstructive Pulmonary Disease (5.3)
- Potentiation of Vascular Insufficiency (5.4)
- Increased Reactivity to Allergens (5.5)
- Potentiation of Muscle Weakness (5.6)
- Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus (5.7)
- Masking of Thyrotoxicosis (5.8)

**ADVERSE REACTIONS**

Most common adverse reactions occurring in approximately 5 to 15% of patients included allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Antihypertensives/cardiac glycosides may lower blood pressure. (7.1)
- Concomitant use with systemic beta-blockers may potentiate systemic beta-blockade. (7.2)
- Oral or intravenous calcium antagonists may cause atrioventricular conduction disturbances, left ventricular failure, and hypotension. (7.3)
- Catecholamine-depleting drugs may have additive effects and produce hypotension and/or marked bradycardia. (7.4)
- Use with CNS depressants may result in an additive or potentiating effect. (7.5)
- Digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. (7.6)
- CYP2D6 inhibitors may potentiate systemic beta-blockade. (7.7)
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine. (7.8)
- Monoamine oxidase inhibitors may result in increased hypotension. (7.9)

**USE IN SPECIFIC POPULATIONS**

- Not for use in children below the age of 2 years. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2011
1 INDICATIONS AND USAGE

COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha-adrenergic receptor agonist with a beta-adrenergic receptor inhibitor indicated for the reduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of 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 including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS, 4).

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)] should, in general, not receive beta-blocking agents, including COMBIGAN®.

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.

5.8 Masking of Thyrotoxicosis

Beta-adrenergic blocking agents may mask signs of thyrotoxicosis. Patients suspected of developing hyperthyroidism should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.9 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 surface, which allowed entry of contaminated water into the container.
epithelial surface (see PATIENT COUNSELING INFORMATION, 17).

5.10 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 resuscitating and heart rate and cardiac arrest have 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.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies 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 edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, infection (primarily conjunctival and respiratory infections), heartburn, insomnia, keratitis, lid disorder, nasal dryness, ocular allergic reaction, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, taste perversion, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

Timolol (Ocular Administration)

Body as a whole: chest pain. Cardiovascular: Angina, chest pain, 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, Immune/G: 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: Acne, angioedema, urticaria, and generalized and localized rash; Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, nasal congestion, respiratory failure; Endocrine: Masked symptoms of hypoglycemia in diabetes patients (see Warnings and Precautions, 5.7); Special Senses: Diplopia, choroidal detachment following filtration surgery, cystoid macular edema, decreased corneal sensitivity, pseudophakoid, ptosis, refractive changes, tinnitus; Urogenital: Decreased libido, impotence, Peyronie’s disease, retroperitoneal fibrosis.

6.2 Postmarketing Experience

Brimonidine

The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, irritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypepotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

Oral Timolol/Oral Beta-blockers

The following additional adverse reactions have been reported in clinical experience with ORAL timolol maleate or 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: Vasodilation, 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, sweat; System/Psychiatric: An acute reversible syndrome characterized by disorientation for time and place, decreased performance on neuropsychometric, diminished concentration, emotional lability, local weakness, reversible mental depression progressing to catatonia, slightly cloudy mental state; Respiratory: Bronchial obstruction, rales; Urogenital: Urination difficulties.

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 orally and COMBIGAN® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

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 atioventricular 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, syncopage, 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 atioventricular conduction time.

7.7 CYP2D6 Inhibitors

Potentially 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 Oxide Inhibitors

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

8.1 Pregnancy

Pregnancy Category C: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (1.65 mg/kg/day) and rabbits (3.33 mg/kg/day) achieved AUC exposure values 580 and 37-fold higher, respectively, than similar values estimated in humans treated with COMBIGAN®, 1 drop in both eyes twice daily.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day [4,200 times the maximum recommended human oculur 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 matemotoxic 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 matemotoxicity.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, COMBIGAN® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

8.3 Nursing Mothers

Timolol has been detected in human milk following oral and ophthalmic drug administration. It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from COMBIGAN® 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.

8.4 Pediatric Use

COMBIGAN® is not recommended for use in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, hypertension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate and timolol maleate have not been studied in children below the age of 2 years.

The safety and effectiveness of COMBIGAN® have been established in the age group 2 – 16 years of age. Use of COMBIGAN® in this age group 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 study, brimonidine tartrate ophthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-83% in patients 2 to 6 years) and decreased alertness. In pediatric patients 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

No information is available on overdosage with COMBIGAN® in humans. There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

11 DESCRIPTION

COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% contains the active ingredients brimonidine tartrate 0.2% and timolol 0.5% with the inactive ingredients benzalkonium chloride 0.005%, sodium phosphate, monobasic; sodium phosphate, dibasic; purified water; and hydrochloric acid and/or sodium hydroxide to adjust pH.

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 glaucomatosus visual field loss. The higher the level of intracocular pressure, the greater the likelihood of glaucomatosus field loss and optic nerve damage.

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

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

Timolol maleate is a beta, and beta, 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 Cmax values of brimonidine were comparable following COMBIGAN® treatment versus monotherapy (32.7 ± 15.0 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 2090 ± 1231 pg•hr/mL, respectively); mean Cmax 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 has not been studied.

**Metabolism**

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

**Excretion**

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

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

**Special Populations**

COMBIGAN® has not been studied in patients with hepatic 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 Cmax 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 adenocarcinomas in female mice at 500 mg/kg/day, (approximately 42,000 times 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 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, compared to placebo.

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 lower (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 tartrate 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 LOPE bottles and tips, with blue high impact polystyrene (HIPS) caps as follows:

<table>
<thead>
<tr>
<th>Volume</th>
<th>Bottle</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mL</td>
<td>10 mL</td>
<td>0023-9211-05</td>
</tr>
<tr>
<td>10 mL</td>
<td>10 mL</td>
<td>0023-9211-10</td>
</tr>
</tbody>
</table>


17 PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product (see CONTRAINDICATIONS, 4).

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions (see WARNINGS AND PRECAUTIONS, 5.9).

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician’s advice concerning the continued use of the present multidose container.

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

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

As with other similar medications, COMBIGAN® may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

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U.S. Patents 6,194,415; 6,465,464; 7,030,149; 7,320,976; 7,323,463, and 7,642,258

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APC67IT11

ALLERGAN
Introducing the Allergan 365 Program

The 365 program is designed to provide you with the education and support you need to better understand your condition and why it is important to use your COMBIGAN® ophthalmic solution each and every day.

As a leader in eye care, Allergan is committed to developing effective therapies for glaucoma patients and to helping educate patients about the disease and the importance of treatment.

1. COMBIGAN® Prescribing Information.
5. Rossi GC, Pasinetti GM, Bracchino M, et al. Switching from concomitant latanoprost 0.005% and timolol 0.5% to a fixed combination of travoprost 0.004%/timolol 0.5% in patients with primary open-angle glaucoma and ocular hypertension: a 6-month, multicenter, cohort study. Expert Opin Pharmacother. 2009;10(11):1705-1711.