IMPORTANT NOTICE

Re: COMBICIG® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

Dispense COMBICIG® as written

When you receive a prescription that specifies COMBICIG®, make sure to dispense as written so the patient receives the medication as prescribed by the Eye Care Professional.

Please do not call our office to request a substitute for COMBICIG® ophthalmic solution.
For your reference, the NDC numbers for COMBICIG® are as follows:

- 5 mL: 0023-9211-05
- 10 mL: 0023-9211-10

COMBICIG® savings offers may be available for patients. Encourage patients to:

- Visit www.Combigan.com to download and print an instant rebate offer
- Ask their Eye Care Professional for coupons and rebates available in the office

INDICATIONS AND USAGE: COMBICIG® (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 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 COMBICIG® dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: COMBICIG® is contra-indicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; in neonates and infants (under the age of 2 years); in patients with a hypersensitivity reaction to any component of COMBICIG® in the past.

WARNINGS AND PRECAUTIONS: COMBICIG® contains timolol maleate. COMBICIG® is administered topically, but can be absorbed systemically. The adverse reactions with systemic administration of beta-adrenergic blocking agents may occur with topical use (eg, severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported with systemic or ophthalmic administration of timolol maleate).

Sympathetic stimulation may be essential to support the circulation in patients with diminished myocardial contractility and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. In patients with no history of cardiac failure, continued depression of the myocardium with beta-blocking agents over time can lead to cardiac failure. Discontinue COMBICIG® at the first sign or symptom of cardiac failure.

Please see additional Important Safety Information on reverse side.
IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued): Patients with chronic obstructive pulmonary disease (eg, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease should not receive beta-blocking agents, including COMBIGAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%.

COMBIGAN® may potentiate syndromes associated with vascular insufficiency. Use caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Patients taking beta-blockers with a history of atopy or 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.

Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia and clinical signs (eg, tachycardia) of hyperthyroidism. Use caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Carefully manage patients that may develop thyrotoxicosis to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Ocular hypersensitivity has occurred with brimonidine tartrate ophthalmic solutions 0.2% (eg, increase in IOP). Some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents due to impairment of beta-adrenergically mediated reflexes during surgery. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

ADVERSE REACTIONS: The most frequent reactions with COMBIGAN® in about 5% to 15% of patients included: allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.

DRUG INTERACTIONS: COMBIGAN® may reduce blood pressure. Use caution in patients on antihypertensives and/or cardiac glycosides.

Observe patients receiving a beta-adrenergic blocking agent orally and COMBIGAN® for additive effects of beta-blockade, both systemic and on intraocular pressure. Concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Use caution in the co-administration of beta-adrenergic blocking agents (eg, COMBIGAN®) and oral or intravenous calcium antagonists due to possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. Avoid co-administration in patients with impaired cardiac function.

Observe patients closely when a beta-blocker is administered to patients receiving catecholamine-depleting drugs (eg, reserpine) due to possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Specific drug interaction studies have not been conducted with COMBIGAN®, but consider the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics). Concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Potentiated systemic beta-blockade (eg, decreased heart rate, depression) has been reported with combined use of CYP2D6 inhibitors (eg, quinidine, SSRIs) and timolol.

Tricyclic antidepressants (TCAs) can blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of TCAs with COMBIGAN® in humans can interfere with the IOP-lowering effect. Caution is advised in patients taking TCAs, which can affect the metabolism and uptake of circulating amines.

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially increase systemic side effect such as hypotension. Use caution in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

Please see accompanying full Prescribing Information.
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COMBIGNAN® (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% is an alpha-2-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 COMBIGNAN® dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of COMBIGNAN® 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.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 2 mg/mL brimonidine tartrate and 5 mg/mL timolol (6.8 mg/mL timolol maleate).

4 CONTRAINDICATIONS

4.1 Asthma, COPD

COMBIGNAN® is contraindicated in patients with 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

COMBIGNAN® 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 (Under the Age of 2 Years)

COMBIGNAN® is contraindicated in neonates and infants (under the age of 2 years).

4.4 Hypersensitivity Reactions

Local hypersensitivity reactions have occurred following the use of different components of COMBIGNAN®. COMBIGNAN® is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

5 WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma

COMBIGNAN® 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 (4.1)].

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, COMBIGNAN® 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 COMBIGNAN® is contraindicated) [see Contraindications (4.1)], should, in general, not receive beta-blocking agents, including COMBIGNAN®.

5.4 Potentiation of Vascular Insufficiency

COMBIGNAN® may potentiate syndromes associated with vascular insufficiency. COMBIGNAN® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, or thromboangitis 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 [see Patient Counseling Information (17)].

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 authors 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.

COMBIGNAN®

In clinical trials of 12 months duration with COMBIGNAN® the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included: allergic conjunctivitis, conjunctival folliculitis, conjunctival hyperemia, eye 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, blepharocconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspnea, dysphoria, fatigue, flu syndrome, follicular conjunctivitis, gastrointestinal disorder, hypercholesterolemia, hypotension, injection (primarily colds and respiratory infections), hordeolum, 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: 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 size and symptoms of myasthenia gravis, insomnia, nightmares, paresthesia, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; Skin: Alopecia, psoas 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), 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, pseudopemphigoid, plicosis, refractive changes, tinnitus; Urogenital: Decreased libido, impotence, Peyronie’s disease, retropositioned fibrosis.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions, timolol ophthalmic solutions, or both in combination, 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, timolol ophthalmic solutions, or a combination of these factors, include: depression, eyelid erythema extending to the cheek or forehead, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, noise, skin reaction, sticking or adhering of lids, eyelid pruritus, redness of eye, redness of photophobia, and somnolence have been reported [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...
8.4 Pediatric Use

COMBIVAN® is contraindicated in children under the age of 2 years [see Contraindications (4.3)]. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hyperthermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving bromidine. The safety and effectiveness of bromidine tartrate and timolol maleate have not been studied in children below the age of 2 years.

The safety and effectiveness of COMBIVAN® have been established in the age groups 2 – 16 years of age. Use of COMBIVAN® in these age groups is supported by evidence from adequate and well-controlled studies of COMBIVAN® in adults with additional data from a study of the concomitant use of bromidine tartrate opthalmic solution 0.2% and timolol maleate opthalmic solution in pediatric glaucoma patients (ages 2 to 7 years). In this study, bromidine tartrate opthalmic solution 0.2% was dosed three times a day as adjunctive therapy to beta-blockers. The most commonly observed adverse reactions were somnolence (50%-63% 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 bromidine tartrate opthalmic 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 overdose with timolol opthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasms, and cardiac arrest. Very limited information exists on accidental ingestion of bromidine in adults alone or in combination. Symptoms of bromidine overdose have been reported in neonates, infants, and children receiving bromidine opthalmic 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

COMBIVAN® (bromidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%, sterile, is a relatively selective alpha-2 adrenergic receptor agonist with a non-selective beta-adrenergic receptor inhibitor (topical intracocular pressure lowering agent).

The structural formulae are:

Bromidine tartrate:

\[
\text{H}_2\text{N}-\text{Br}
\]

Timolol maleate:

\[
\text{H}_2\text{N}-\text{Br}
\]

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

Timolol maleate:

\[
\text{H}_2\text{N}-\text{COOH}
\]

In solution, COMBIVAN® (bromidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% has a green, greenhouse-yellow color. It has an osmolality of 260-330 mOsm/kg and a pH during its shelf life of 6.5-7.3.

Bromidine 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.

Each mL of COMBIVAN® contains the active ingredients bromidine 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

COMBIVAN® is comprised of two components: bromidine tartrate and timolol. Each of these two components decreases elevated intracocular pressure, whether or not associated with glaucoma. Elevated intracocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the...
level of intracranial pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

**COMBIMAX** 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, 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 **COMBIMAX**. Normal volunteers dosed with one drop of **COMBIMAX** 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 **COMBIMAX** 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 **COMBIMAX** was 129 ± 61 pg·hr/ml versus 141 ± 108 pg·hr/ml for the respective monotherapy treatments; mean Cmax values of brimonidine were comparable following **COMBIMAX** treatment versus monotherapy (32.7 ± 15 pg/ml versus 34.7 ± 26.2 pg/ml, respectively). Mean timolol AUC for **COMBIMAX** was similar to that of the respective monotherapy treatment (2591 ± 1679 pg·hr/ml versus 2509 ± 1233 pg·hr/ml, respectively); mean Cmax of timolol was approximately 20% lower following **COMBIMAX** treatment versus monotherapy.

In a parallel study in patients dosed twice daily with **COMBIMAX** 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 **COMBIMAX** than their respective monotherapy values. The lower plasma brimonidine concentrations with **COMBIMAX** appears to be due to twice-daily dosing for **COMBIMAX** 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 67% of an orally-administered radioactive dose of brimonidine was eliminated within 12 hours, with 74% found in the urine. Unchanged timolol and its metabolites are excreted by the kidney.

#### Special Populations

**COMBIMAX** has not been studied in patients with hepatic impairment.

**COMBIMAX** 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 concentrations in humans treated with one drop of **COMBIMAX** 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 adenocarcinoma of the large intestine in male rats administered 300 mg/kg/day (approximately 20,000 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 treated with oral doses equivalent to approximately 8,300 times the daily dose of **COMBIMAX** 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), but not at 150 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 50 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 doses up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

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, cyogenetic study, and dominant lethal assay.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the microcrucial test and genotoxic assay (doses up to 800 mg/kg) and in vitro in a necaplastic 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.

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 **COMBIMAX**.

### 14 CLINICAL STUDIES

Clinical studies were conducted to compare the IOP-lowering effect over the course of the day of **COMBIMAX** 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. **COMBIMAX** BID provided an additional 1.5 mm Hg decrease in IOP over brimonidine tartrate 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 effect of **COMBIMAX** 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. **COMBIMAX** 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

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

- 5 ml in 10 ml bottle: NDC 0023-9211-05
- 10 ml in 10 ml bottle: NDC 0023-9211-10

**Storage:** Store at 15°–25°C (59°–77°F). Protect from light.

### 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 (4.1, 4.2)].

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 blindness may result from using contaminated solutions [see Warnings and Precautions (5.10)]. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

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 **COMBIMAX** 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 reininserted 15 minutes following administration of **COMBIMAX**.

As with other similar medications, **COMBIMAX** 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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Patiens. See: www.allergan.com/products/patent_notices

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