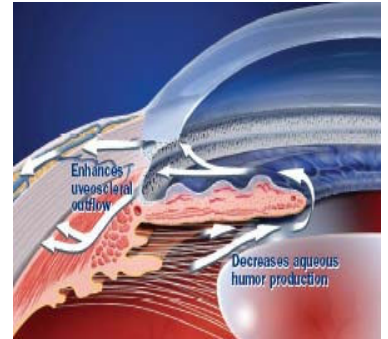




## COMBIGAN™ Fact Sheet

### About COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%

COMBIGAN™ offers eye care professionals an effective and well-tolerated adjunctive therapy for patients who require additional IOP lowering. COMBIGAN™, approved by the U.S. Food and Drug Administration in 2007, 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 COMBIGAN™ ophthalmic solution 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.<sup>1</sup>



### How COMBIGAN™ Works

One of the risk factors of glaucoma is elevated IOP, or pressure inside the eye. A healthy eye produces fluids, called aqueous humor, at the same rate fluids are drained. If the aqueous humor is not removed rapidly enough or the eye fills too rapidly, pressure builds up in the eye, which can result in glaucoma. COMBIGAN™ ophthalmic solution provides a dual mechanism of action to lower IOP by reducing production of aqueous humor, the fluid in the eye that fills the space between the cornea and iris, and enhancing aqueous humor drainage via the uveoscleral pathway.<sup>1</sup>

### COMBIGAN™ Benefits

- Clinical data indicates that COMBIGAN™ ophthalmic solution is an effective adjunct to a prostaglandin analogue, a class of drugs often used as first-line therapy for elevated IOP. Results from pooled three-month studies found that COMBIGAN™ significantly reduced mean IOP up to 29 percent (6.9 mm Hg) from baseline when added to a prostaglandin analogue (demonstrated in 37 patients).<sup>2</sup>
- COMBIGAN™ ophthalmic solution is an effective next step for beta-blocker patients who require additional IOP reduction. A 12-week clinical trial resulted in an additional mean IOP reduction of 25 percent (5.7 mm Hg) from a timolol (beta-blocker) baseline (demonstrated in 121 patients).<sup>3</sup>
- Results from pooled three-month studies found that COMBIGAN™ reduced mean IOP to 15.6 mm Hg versus a reduction to 17.2 mm Hg with Cosopt® at three months (demonstrated in 101 patients).<sup>2</sup> Also, COMBIGAN™ ophthalmic solution demonstrated low burning and stinging, and 91 percent of patients reported that COMBIGAN™ was comfortable or very comfortable (demonstrated in 85 patients).<sup>4</sup>
- Glaucoma patient compliance is affected by multiple factors including the number of agents a patient is taking.<sup>5,6,7,8</sup> Many patients require more than one medication to meet their target IOP. COMBIGAN™ ophthalmic solution offers the IOP-lowering efficacy of two proven agents in the convenience of one bottle.



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## **COMBIGAN™ Efficacy**

In the 12-month pivotal trials of 1,159 patients, COMBIGAN™ ophthalmic solution significantly reduced mean IOP up to 33 percent (7.6 mm Hg) from baseline and was well tolerated with a low ocular allergy rate of 5.2 percent (demonstrated in 385 patients).<sup>9</sup>

## **About Glaucoma**

Glaucoma, a group of eye diseases characterized by damage to the optic nerve, is the leading cause of preventable blindness in the United States.<sup>10</sup> It is estimated that three million Americans have glaucoma, but only half of those know they have it.<sup>11</sup> The total number of glaucoma cases worldwide is estimated to be 65 million.<sup>11</sup> One of the risk factors of glaucoma is elevated IOP, or pressure inside the eye. A healthy eye produces fluids, called aqueous humor, at the same rate fluids are drained. If the aqueous humor is not removed rapidly enough or the eye fills too rapidly, pressure builds up in the eye, which can result in glaucoma. This high pressure distorts the shape and damages the optic nerve. Maintaining healthy IOP levels may slow the progression of the disease and help prevent vision loss.

## **About Timolol**

Timolol and other beta-blockers are indicated for the first-line treatment of elevated IOP in patients with ocular hypertension and open-angle glaucoma.

## **Important COMBIGAN™ Safety Information:**

**Contraindications:** COMBIGAN™ ophthalmic solution is contraindicated 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, cardiogenic shock; and in patients with hypersensitivity to any component of this product.

**Warnings and Precautions:** Severe respiratory reactions including death due to bronchospasm in patients with asthma have been reported following systemic or ophthalmic administration of timolol maleate. Sympathetic stimulation may be essential in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe cardiac 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. Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease should, in general, not receive beta-blocking agents, including COMBIGAN™. COMBIGAN™ may potentiate syndromes associated with vascular insufficiency. While taking beta-blockers, patients may be more reactive to allergens. Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms. Beta-adrenergic receptor blocking agents may mask hypoglycemic symptoms in patients with diabetes mellitus. 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.

**Adverse reactions:** The most common adverse reactions occurring in approximately 5 to 15% of patients included allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, and ocular burning and stinging.

**Drug interactions:** Antihypertensives/cardiac glycosides may lower blood pressure. Concomitant use with systemic beta-blockers may potentiate systemic beta blockade. Oral or intravenous calcium antagonists may cause atrioventricular conduction disturbances, left ventricular failure, and hypotension. Catecholamine-depleting drugs may have additive effects and produce hypotension and/or marked bradycardia. Use with CNS depressants may result in an additive or potentiating effect. Digitalis and calcium antagonists may have additive effects in prolonging atrioventricular

conduction time. CYP2D6 inhibitors may potentiate systemic beta-blockade. Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine. Monoamine oxidase inhibitors may result in increased hypotension.

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### Additional Information

For more information about COMBIGAN™ ophthalmic solution, please refer to the full prescribing information and the product Web site at [www.combigan.com](http://www.combigan.com).

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<sup>1</sup> COMBIGAN™ prescribing information.

<sup>2</sup> Nixon D. Evaluation of the Tolerability and Efficacy of Brimonidine Tartrate 0.2% - Timolol Maleate 0.5% Ophthalmic Solution (COMBIGAN™) and Dorzolamide Hydrochloride 2% - Timolol Maleate 0.5% Ophthalmic Solution (Cosopt®) in Patients with Open-Angle Glaucoma or Ocular Hypertension. Poster presented at: 17th Annual Meeting of the American Glaucoma Society; March 1-4, 2007, San Francisco.

<sup>3</sup> Goni FJ and the Brimonidine/Timolol Fixed Combination Study Group. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. *Eur J Ophthalmol*. 2005;15(5):581-590.

<sup>4</sup> Nixon DR, Hollander DA. Comparison of the efficacy and tolerability of twice-daily COMBIGAN versus Cosopt® fixed-combination therapies. Poster presented at 111<sup>th</sup> Annual Meeting of the American Academy of Ophthalmology; November 10-13, 2007; New Orleans, LA.

<sup>5</sup> Robin A, Covert, D. Does Adjunctive Glaucoma Therapy Affect Adherence to the Initial Primary Therapy? *Ophthalmology*. 2005.

<sup>6</sup> Patel S, Spaeth, G. Compliance in Patients Prescribed Eye Drops for Glaucoma. *Ophthalmic Surg*. 1995.

<sup>7</sup> Olthoff C, Schouten, A, et al. Noncompliance with Ocular Hypotensive Treatment in Patients with Glaucoma or Ocular Hypertension *Ophthalmology*. 2005.

<sup>8</sup> Stewart W, Konstas, A, Pfeiffer, N. Patient and Ophthalmologist Attitudes Concerning Compliance and Dosing in Glaucoma Treatment. *J Ocul Pharmacol Ther*. 2004.

<sup>9</sup> Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5%/timolol fixed-combination therapy vs. monotherapy with timolol or brimonidine in patients with glaucoma and ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol*. 2006; 124(9): 1230-1238.

<sup>10</sup> The Glaucoma Foundation. "TGF Urges Eye Exams to Detect the Disease Early" January 8, 2006. [http://www.glaucomafoundation.org/news\\_story.php?i=38](http://www.glaucomafoundation.org/news_story.php?i=38). Accessed April 19, 2007.

<sup>11</sup> Glaucoma Research Foundation. "Glaucoma Facts and Stats" Available at: [http://www.glaucoma.org/learn/glaucoma\\_facts.html](http://www.glaucoma.org/learn/glaucoma_facts.html). Accessed: July 31, 2007.