**INSTRUCTIONS FOR USE**

1. **Tighten** the cap on the nozzle by turning it clockwise. The cap will make a clicking sound. Turn the cap in the opposite direction to remove it.

2. **Remove** the cap, by turning it in the opposite direction. The bottle is now ready for use. **Do not** twist the bottle. The dose may be delivered either into the eyelid or conjunctival sac, or into the inferior or superior fornix of the eye.

3. **Do not** touch the bottle or the nozzle of the bottle.

4. **Replace** the cap. **Do not** press the bottle. The eye must be closed for 15 seconds after each drop to allow sufficient time for the medication to be absorbed.

5. **State of the art technology**

   **From Allergan India Private Limited**

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**BRIMONIDINE TARTRATE + TIMOLOL MALEATE OPHTHALMIC SOLUTION**

**Combigan™**

**DESCRIPTION**

Combigan™ (Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution) is a selective alpha-2 adrenergic receptor blocking agent with a non-selective beta-adrenergic receptor blocking agent (topical antimuscarinic agent).

**Brimonidine Tartrate**

**Timolol Maleate**

**Empirical Formula**

CH₁₇H₂₀NO₅.G₃H₂O

C₁₅H₁₇NO₄.G₃H₂O

**Molecular Weight**

442.24 as the tartrate salt

452.30 as the maleate salt

**Chemical Name**

S-(2-Amino-1,3-benzodioxol-5-yl)phenyl-2-(m-phenylphenylamino)acetate (Brimonidine Tartrate)

S-(2-Aminobenzyl)benzyltrimethanol (Timolol Maleate)

**Appearance**

Offwhite, or white to off-white powder

White, odorless, amorphous, or crystalline powder

**Solubility**

Soluvents in both water (1.0 mg%), and in the product vehicle (2.0 mg%) at pH 7.0

Soluvents in water, methanol, and alcohol.

**Mechanism of action**

Combigan™ is comprised of two components: Brimonidine Tartrate and Timolol Maleate. Each of these two components decreases elevated intracranial pressure, whether or not associated with glaucoma. Elevated intracranial 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 risk of glaucomatous visual field loss and optic nerve damage.

Combigan™ is a selective alpha-2 adrenergic receptor with a non-selective beta-adrenergic receptor blocking agent. Both brimonidine and timolol have a rapid onset of action, which is due to their opposite effects on the alpha and beta adrenergic receptors.

**INDICATIONS AND USAGE**

Combigan™ (brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5%) is indicated for reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who are inadequately responsive to topical beta blockers.
CONTAINMENT/INHALE

Contraindicated in patients with (1) bronchial asthma, (2) a history of bronchial asthma, (3) severe chronic obstructive pulmonary disease (see WARNINGS), (4) severe bronchitis, (5) severe or third degree atelectasis, (6) severe cardiac failure (see WARNINGS), (7) constrictive pericarditis, (8) in patients receiving nonsteroidal anti-inflammatory drugs, (9) by hyperosmolarity in any component of the medication.

WARNINGS

As with many topical asthmatic inhalation drugs, this drug is absorbed systemically. The same type of adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of Cilengitide. 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 topical administration of timolol (see CONTRAINDICATIONS).

Cilengitide causes symmetric slowing of the respiration, and its effect on the respiratory system may be potentiated by concomitant beta-blockers. This is due to the inhibition of beta-1-agonist receptors in the respiratory tract, which may result in increased airway resistance.

In patients with a history of cardiac failure, prolonged depression of the myocardium with beta-blocking agents may lead to an increase in the risk of cardiac failure. In patients with a history of chronic obstructive pulmonary disease, prolonged depression of the myocardium with beta-blocking agents may lead to an increase in the risk of cardiac failure.

Cilengitide must be administered with caution in patients with a history of cardiac failure, chronic obstructive pulmonary disease, or chronic bronchitis, or in patients with a history of chronic obstructive pulmonary disease, or chronic bronchitis, or in patients with a history of chronic obstructive pulmonary disease, or chronic bronchitis.

Cilengitide is contraindicated in patients with (1) bronchial asthma, (2) a history of bronchial asthma, (3) severe chronic obstructive pulmonary disease (see WARNINGS), (4) severe bronchitis, (5) severe or third degree atelectasis, (6) severe cardiac failure (see WARNINGS), (7) constrictive pericarditis, (8) in patients receiving nonsteroidal anti-inflammatory drugs, (9) by hyperosmolarity in any component of the medication.

DRUG INTERACTIONS

Asthmatics/bronchitics/glaucoma. Because Cilengitide may reduce blood pressure, caution in using drugs such as antihypertensives and/or diuretics is advised.

Beta-adrenergic blocking agents. Patients who are receiving a beta-adrenergic blocking agent orally and Cilengitide should be observed for potential additive effects of beta-blockers, both systemic and ophthalmic. Therefore, the concurrent use of two topical beta-adrenergic blocking agents is not recommended.

Cycloplegics. Cilengitide should be used in the combination of ocular anesthetics, such as Cilengitide and/or ophthalmic anesthetics because of possible anesthetic drug interactions, irritation, reduced aqueous humor production, and reduced aqueous humor pressure, which may result in vertigo, syncope, or opthalmoplegia.

CNS depressants. Although specific drug interaction studies have not been conducted with Cilengitide, the possibility of an additive or potentiating effect on CNS depressants (e.g., alcohol, barbiturates, opioids, anesthetics, or anticholinergic) should be considered.

Cigarette smoking. Cilengitide should be used in the combination of ocular anesthetics, such as Cilengitide and/or ophthalmic anesthetics because of possible anesthetic drug interactions, irritation, reduced aqueous humor production, and reduced aqueous humor pressure, which may result in vertigo, syncope, or opthalmoplegia.

CNS depressants. Although specific drug interaction studies have not been conducted with Cilengitide, the possibility of an additive or potentiating effect on CNS depressants (e.g., alcohol, barbiturates, opioids, anesthetics, or anticholinergic) should be considered.

Digitalis and sedative antihistamines. The concurrent use of beta-adrenergic blocking agents with digitalis and sedative antihistamines may have additive effects in producing antiallergic or antihistaminic action.

Digoxin. Prolonged systemic beta blockade (e.g., decreased heart rate) has been reported during combined treatment with Cilengitide and beta-blockers because beta-blockers inhibit the metabolism of Cilengitide to the more active beta-1 antagonist.

Drugs with antiarrhythmic effects. Drug interactions with antiarrhythmic effects may potentiate the antiarrhythmic effect of Cilengitide.

Drug interactions with beta-blockers. Combined beta-blockers may potentiate the antiarrhythmic effect of Cilengitide.

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