

SAFETY DATA SHEET

SECTION 1: PRODUCT IDENTIFICATION

Compound Name: **COMBIGAN® (Brimonidine Tartrate, 0.2%/Timolol, 0.5%) Ophthalmic Solution**

Chemical Class: Alpha Adrenergic Receptor Agonist/ Beta-Adrenergic Receptor Blocking Agent

Recommended Use: Pharmaceutical

Manufacturer's Name: Allergan Australia Pty Ltd

Address: 810 Pacific Highway
Gordon NSW 2072 Australia

Telephone: 612-9498-0100 (Monday – Friday 9 am – 5 pm)
131 126 (24 hours, within Australia) – Poison Information Centre

Revision Date: September 1, 2011 (*Supersedes* October 2, 2007)

SECTION 2: HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW: COMBIGAN® (Brimonidine Tartrate, 0.2%/Timolol, 0.5% Ophthalmic Solution may cause mild to moderate irritation of the eyes in sensitive individuals. If irritation persists, seek medical attention. As with other beta-adrenergic blocking agents, inadvertent overdose or overexposure to timolol maleate may cause dizziness, headache, shortness of breath, bronchospasm, heart rhythm abnormalities, or cardiac arrest. If symptoms develop, seek medical attention immediately.

Hazard Classification (GHS): Target organ systemic toxicity – Repeated exposure (Category 2)

Signal Word and Hazard Statements (GHS): Warning – May cause heart rhythm abnormalities through prolonged or repeated exposure.

Risk / Safety Phrase: None allocated. Not hazardous per Approved Criteria for Classifying Hazardous Substances [NOHSC:1008]



Potential Health Effects:

EYE CONTACT: Contact with the eyes may result in mild to moderate transient irritation (burning or stinging) in sensitive individuals. Avoid unintentional contact with the eyes. Overdose or overexposure may result in symptoms associated with beta-adrenergic blocking agents. These may include: headache; dizziness; fatigue; chest pain; nausea; breathing difficulty and cardiac abnormalities.

SKIN CONTACT: Prolonged contact with the skin may result in mild irritation. Topical exposure to timolol maleate may result in systemic absorption, producing symptoms as described above.

INHALATION: The product is non-volatile and inhalation is not likely to occur.

INGESTION: May cause irritation and sedation. At extremely high doses (equivalent to several 15 mL bottles) may cause nausea, headache and confusion. May produce stomach upset and nausea. May be absorbed systemically, resulting in symptoms described above. Significant overexposure may result in heart block or cardiac arrest.

CHRONIC EFFECTS: Repeated ocular use in humans has been shown, in some cases, to produce oral dryness, eye irritation, ocular allergic reactions, headache or fatigue/drowsiness. Caution should be exercised in use by persons with severe cardiovascular disease. Persons chronically exposed to timolol maleate should be periodically monitored for pulmonary abnormalities as well as cardiac irregularities.

Brimonidine tartrate has been shown to produce ocular allergies in sensitive individuals (fewer than 10 % of all clinical subjects).

No carcinogenic effects were observed when tested in mice and rats. No embryotoxic or teratogenic effects were observed when tested in rats or rabbits at doses in excess of 300 times (rats) and 24 times (rabbits) the anticipated human exposure. No ingredient in this product is regulated or listed as a carcinogen by OSHA, IARC, or NTP.

SECTION 3: COMPOSITION/HAZARDOUS INGREDIENTS

Chemical Name	CAS Number	Percent (By Weight)	Exposure Limits in Air (8 hr. TWA)		
			OSHA PEL	ACGIH TLV	ALLERGAN OEL
Brimonidine Tartrate	70359-46-5	0.2	N/E	N/E	12.5ug/m ³
Timolol Maleate, USP	26921-17-5	0.68 (1)	N/E	N/E	N/E
Sodium Phosphate dibasic, heptahydrate	7782-85-6	2.5	N/E	N/E	N/E

Note (1): Equivalent to 0.50% Timolol free base

SECTION 4: FIRST AID MEASURES

- Eye Contact:** If irritation persists, flush eyes with plenty of water for at least 15 minutes. Obtain medical attention if irritation or other symptoms persist.
- Skin Contact:** Wash skin thoroughly with soap and water. If irritation develops consult a physician. Wash contaminated clothing before reuse.
- Inhalation:** Inhalation is not likely to occur. If symptoms occur, move to fresh air and obtain medical attention. Treat symptomatically.
- Ingestion:** Seek medical attention immediately. Treatment of an oral overdose includes supportive and symptomatic therapy. Patients should be monitored for signs or symptoms associated with exposure to beta-adrenergic blocking agents including breathing abnormalities, heart irregularities or cardiopulmonary insufficiencies.

SECTION 5: FIRE FIGHTING MEASURES

- Flash Point and Method:** Greater than 200°F (Seta Flash Cup)
- Flammable Limits:** Not applicable
- Autoignition Temperature:** No data for this product
- Fire-Extinguishing Materials:** Material is non-flammable. Use extinguishing media suitable for materials supporting combustion such as water fog, CO₂, foam or dry chemical
- Fire fighting Procedures:** Use self-contained breathing apparatus in enclosed or confined spaces or as otherwise needed.
- Unusual Fire and Explosion Hazards:** None known

SECTION 6: ACCIDENTAL RELEASE MEASURES

Wipe up spilled liquid with absorbent material and wash area with water. If large quantities are spilled, flush spill area with water.

SECTION 7: HANDLING AND STORAGE

Handling: Avoid unintentional contact with skin surfaces. Wash thoroughly after handling. Observe all precautions contained on product label and package insert..

Storage: Store in a cool, dry location out of direct sunlight. Keep container closed when not in use.

SECTION 8: EXPOSURE CONTROLS AND PERSONAL PROTECTION

Engineering Controls: None necessary for normal product handling.

Respiratory Protection: None necessary for normal product handling.

Eye Protection: None required for normal product handling. If responding to a spill situation, use safety glasses with side shields.

Protective Clothing: None required for normal product handling. Use latex or chemical resistant gloves and other protective clothing as necessary to avoid liquid contact during spill response.

Hygienic Work Practices: Wash hands thoroughly after handling. If working with large quantities of liquid (such as spill clean-up), use latex or chemical resistant gloves and appropriate eye protection. No eating, drinking or smoking in area.

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

Appearance and Odor: Clear, light yellow liquid with slight odor

pH: 6.8 – 7.0

Melting Point/ Freezing Point: Not Determined

Boiling Point: >100° C (>212° F)

Vapor Pressure (mm Hg at 20° C): No data for this product

Vapor Density (Air = 1): No data for this product

Solubility in Water: Soluble

Specific Gravity: Approximately 1.0

Partition coefficient: n-octanol/water: Not Determined

SECTION 10: STABILITY AND REACTIVITY

General: This product is stable and hazardous polymerization will not occur.

Incompatible Materials and Conditions to Avoid: Store away from oxidizers and heat. Store below 25 °C.

Hazardous Decomposition: None known

SECTION 11: TOXICOLOGICAL INFORMATION

Oral: The oral LD50 for Brimonidine Tartrate was determined to be 50 mg/kg in mice and 100 mg/kg in rats, equivalent in dosage to 25 g/kg in mice and 50 g/kg in rats of **COMBIGAN® Ophthalmic Solution**. Incidence of mortality was not consistent, and was apparently due to hypothermia and starvation. Clinical signs included sedation, ataxia, prostration, ptosis, reduced blink reflex, hypotension, hypothermia, respiratory depression/arrest, and circulatory collapse. At a dose of 3.0 mg/kg (equivalent to one 15 mL bottle ingested by a

10 kg child), no clinical signs of toxicity were observed in mice or rats. At a dose of 10 mg/kg (equivalent to three bottles), transient decreased motor activity, ataxia and/or prostration were observed in both species.

Oral administration of Brimonidine Tartrate for one year in rats resulted in toxicity only at the high dose (1.0 mg/kg/day). All changes were reversible within the 8 week recovery period. In monkeys, administration of Brimonidine Tartrate for one year resulted in sedation, slight hypotension, sinus bradycardia, and occasionally, sinus arrhythmia at a dose of 2.5 mg/kg/day. No observable effects were noted at a dose of 0.1 mg/kg/day

The oral LD₅₀ for timolol maleate is reported to be 1028 mg/kg in rats and 1137 mg/kg in mice. In other studies, significant lethality was observed in female rats and female mice after a single dose of 900 and 1190 mg/kg of timolol, respectively. No details of the toxic effects were reported. A thirty year old human female who ingested 650 mg of timolol maleate tablets experienced second and third degree heart block. After recovery she subsequently developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate and borderline first degree heart block.

Ocular: Brimonidine Tartrate at varying concentrations was administered in repeated doses (one drop into one eye twice per day) to rabbits for six months and monkeys for one year. Rabbits exhibited dose-dependent sedation at the 0.5 % concentration but not at the 0.2% concentration. Monkeys treated with up to 0.8% solution showed no local or systemic effects.

In human clinical trials, brimonidine tartrate ophthalmic solution, 0.2% was administered twice per day for one year. The most frequent adverse events, in descending order, were oral dryness, ocular hyperemia, burning/stinging, blurring, headache, fatigue/drowsiness, eye irritation and ocular allergies. No clinically significant changes in heart rate or blood pressure were measured in the treatment group.

There are reports of patients developing ocular symptoms (burning, conjunctivitis, discharge and stinging) and systemic symptoms (headache, dizziness, bradycardia) after timolol maleate administration at the therapeutic dose. Persons with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema), bronchospastic disease, bronchial asthma, or history of cardiac disease should not be exposed to **COMBIGAN[®] Ophthalmic Solution**.

Reproduction: In reproduction studies performed in rats at oral doses more than 100 times (0.66 mg base/kg) the plasma drug concentration in humans receiving multiple ophthalmic doses, brimonidine tartrate produced no evidence of impaired fertility or harm to the fetus. For timolol maleate, no teratogenic or reproductive effects were observed in mice, rats and rabbits at doses up to 50 mg/kg/day (7,000 times the maximum recommended human ophthalmic dose). Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Mutagenicity: Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay. Timolol maleate was negative when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 µg/mL). Ames testing was negative in three of the four strains tested. In the fourth strain tested (TA100), no consistent dose response relationship was seen, nor did the ratio of test to control revertants reach the criteria for positive Ames test, and therefore the overall result was considered negative.

SECTION 12: ECOLOGICAL INFORMATION

No ecological information is available for the product.

SECTION 13: DISPOSAL CONSIDERATIONS

For small quantities of **COMBIGAN[®] Ophthalmic Solution**, discard as ordinary trash. For large quantities, contact Allergan for information on disposal options.

SECTION 14: TRANSPORT INFORMATION

Not a hazardous material for DOT, IATA, IMO or TDG shipment.

SECTION 15: REGULATORY INFORMATION

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008 (2004)]: Not hazardous

List of Designated Hazardous Substances (Australia): Not listed

Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP): None Allocated

TSCA (Toxic Substances Control Act):

As defined by U.S. Code Title 15, Chapter 53 (TSCA), Section 2602 and TSCA Regulations at 40CFR, Subchapter R, Part 710, this drug product is exempt from regulations under TSCA.

CERCLA (Comprehensive Environmental Response, Compensation, and Liability Act):

This product contains no components subject to reporting or notification requirements.

SARA Title III (Superfund Amendments and Reauthorization Act):

311/312 Hazard Categories: Immediate Health

313 Reportable Ingredients: None

WHMIS (Workplace Hazardous Materials Information System - Canada):

Not Regulated (Product is regulated by the Food and Drugs Act)

SECTION 16: OTHER INFORMATION

Revision Summary: Revised September 1, 2011 (Supersedes October 2, 2007)

The preceding information is based on available data and is believed to be correct. However, no warranty is expressed or to be implied regarding the accuracy of this information, the results to be obtained from the use thereof or the hazards connected with the use of the material. Since the information contained herein may be applied under conditions beyond our control and with which we may be unfamiliar, Allergan does not assume any responsibility for the results of its use. This information is furnished upon the condition that the persons receiving it shall make their own determinations of the effects, properties, and protections which pertain to their particular conditions.