



Dorzolamide Hydrochloride – Timolol Maleate Ophthalmic Solution (Sterile)
MATERIAL SAFETY DATA SHEET

Effective Date: 2/27/07

Supersedes: None

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Section 1: CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Product Name: Dorzolamide Hydrochloride – Timolol Maleate Ophthalmic Solution (Sterile)

Product Code(s): Core 486

NDC 24208-486-05 (5 ml)

NDC 24208-486-10 (10 ml)

For Information: 1-800-553-5340

For Emergency: 1-800-535-5053

Chemical Family: Carbonic Anhydrase Inhibitor / Beta-Adrenergic Receptor Blocker

Manufacturer: Bausch & Lomb, Incorporated

Address: 1400 N. Goodman Street
 Rochester, New York 14609

Section 2: COMPOSITION / INFORMATION ON INGREDIENTS

CAS #	COMPONENT NAME	% W/W	OCCUPATIONAL EXPOSURE LIMITS / GUIDELINES										UNITS	
			OSHA PEL TWA /STEL	ACGIH TLV TWA /STEL	NIOSH REL TWA /STEL	IRELAND TWA /STEL	HSE TWA /STEL							
130693-82-2	Dorzolamide Hydrochloride	2	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
26921-17-5	Timolol Maleate	0.5	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
6132-04-3	Sodium Citrate Dihydrate, USP	< 1	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
9004-62-0	Hydroxyethyl Cellulose	< 1	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
69-65-8	Mannitol	< 3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
63449-41-2	Benzalkonium Chloride	0.0075	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
7732-18-5	Purified Water	Bal.	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NA
TOTAL		100***												

N/E: Not Established OSHA: Occupational Safety & Health Administration
 N/A: Not Applicable PPM: Parts Per Million
 ACGIH: American Conference of Governmental Industrial Hygienists
 NIOSH: National Institute for Occupational Safety & Health

TWA: 8-Hour Time-Weighted Average
 STEL: Short-Term Exposure Limit
 C: Ceiling Limit
 REL: Recommended Exposure Limit

* Total Mist
 ** Respirable Mist
 *** pH balanced with sodium hydroxide

Section 3: HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Caution!! Pharmacologically Active Material. Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is a carbonic anhydrase inhibitor and a beta-adrenergic receptor blocker formulated for topical ophthalmic use. It is indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma who are insufficiently responsive to beta-blockers. Dorzolamide Hydrochloride – Timolol Maleate Ophthalmic Solution contains both a sulfonamide and a beta-adrenergic blocking agent; and although administered topically, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. Do Not Use: if there exists hypersensitivity to any ingredient in this product. WARNING: Keep out of reach of children.

Section 3: HAZARDS IDENTIFICATION (cont.)

PRECAUTIONS:

Caution!! Pharmacologically Active Material.

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is a carbonic anhydrase inhibitor and a beta-adrenergic receptor blocker formulated for topical ophthalmic use. It is indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma who are insufficiently responsive to beta-blockers. Dorzolamide Hydrochloride – Timolol Maleate Ophthalmic Solution contains both a sulfonamide and a beta-adrenergic blocking agent; and although administered topically, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration.

Do Not Use: if there exists hypersensitivity to any ingredient in this product.

Use only in accordance with product prescribing information.

WARNING: Keep out of reach of children.

POTENTIAL HEALTH EFFECTS

EYE:

In clinical studies, Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution was generally well tolerated; no adverse experiences peculiar to this combination drug have been observed. The most frequently reported drug-related ocular side effects and local symptoms were burning/stinging, taste perversion, corneal erosion, conjunctival injection, blurred vision, tearing, and ocular itching. Urolithiasis was reported rarely. For additional documentation, refer to the product prescribing information.

SKIN:

No data are available for the finished product. Dorzolamide Hydrochloride Ophthalmic Solution 2% showed no evidence of sensitization in the guinea pig maximization test (GPMT) and the Buehler test.

INGESTION:

No data available with regard to human over dosage by accidental or deliberate ingestion of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution. May be harmful if swallowed.

The most common signs and symptoms to be expected with over dosage of dorzolamide hydrochloride are electrolyte imbalance, development of an acidotic state, and possible central nervous system effects.

There have been reports of inadvertent over dosage with timolol maleate 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.

INHALATION:

No data available. Unlikely to be hazardous when used as directed. May be irritating to the respiratory tract.

CHRONIC HEALTH EFFECTS

Dorzolamide Hydrochloride and Timolol Maleate: No adverse were seen in rabbits and dogs treated topically with dorzolamide hydrochloride and timolol maleate ophthalmic solution in studies lasting 3 and 6 months, respectively.

Section 3: HAZARDS IDENTIFICATION (cont.)

No adverse ocular effects were seen in monkeys and rabbits treated topically with 2% dorzolamide hydrochloride and 0.5% timolol maleate ophthalmic solutions administered concomitantly in studies lasting 15 days and 1 month, respectively.

Dorzolamide Hydrochloride: Dorzolamide hydrochloride is a potent carbonic anhydrase inhibitor used to reduce elevated intraocular pressure. In repeat-dose studies the following effects were observed: a number of bladder and renal histologic changes in mice and rats; upper gastric tract, metabolic acidosis, bone changes and minor decreases in erythroid parameters in dogs and monkeys. The lowest no-effect level for these changes, most of which were considered secondary to the pharmacological activity of dorzolamide, was 0.05 mg/kg/day (2.5 mg for a 50 kg person).

Developmental toxicity (e.g., malformations of the vertebral bodies) was observed in the presence of maternal toxicity in rabbits with a no-effect level of 1 mg/kg/day. It is excreted in breast milk and has caused delayed development in nursing animals. It did not affect the reproductive system of male and female rats at very high doses.

In a 2-year oral toxicity study, urinary bladder papillomas in male rats at 20 mg/kg/day were observed. This is considered a drug class-effect in rats. Papillomas were not observed in female rats or in mice (both sexes). No bladder changes were observed in dogs or monkeys treated up to one year.

There was no evidence of mutagenic or genotoxic potential in a battery of *in vitro* and *in vivo* assays.

Timolol Maleate: No adverse ocular effects were observed in rabbits and dogs administered timolol maleate ophthalmic solution topically in studies lasting 1 and 2 years, respectively.

CARCINOGENICITY:

NTP: No ingredients listed.

IARC: No ingredients listed.

OSHA: No ingredients listed.

MEDICAL CONDITIONS AGGRAVATED BY OVEREXPOURE:

Allergic reactions, severe renal (kidney) impairment, cardiac disease, asthma and chronic obstructive lung disease.

Section 4: FIRST AID MEASURES

EYES:

If discomfort or irritation develops, immediately discontinue product use and contact your eye care professional. For accidental and non-therapeutic applications, flush eyes with copious amounts of water for at least 15 minutes. Get medical attention if irritation occurs.

SKIN:

Wash contaminated area with soap and water. Get medical attention if irritation develops.

INGESTION:

Do NOT Induce Vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this product are swallowed, call a physician immediately. Provide product-prescribing information.

Section 4: FIRST AID MEASURES (cont.)

INHALATION:

No inhalation exposure expected with this formulation under normal conditions. If inhaled, remove to fresh air. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Get medical attention if symptoms appear.

ADDITIONAL NOTES TO PHYSICIAN:

This formulation contains a sulfonamide (dorzolamide hydrochloride) and a beta-adrenergic blocking agent (timolol maleate), which are absorbed systemically. Reactions common to these classes of materials may occur (cardiac, respiratory and hypersensitivity, etc.).

For additional guidance, refer to the product-prescribing information. Contact the local Poison Control Center.

Section 5: FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES:

Flash Point: Not Applicable

Method: NA

EXTINGUISHING MEDIA:

Water spray, carbon dioxide, dry chemical powder or appropriate foam for surrounding fire.

HAZARDOUS COMBUSTION PRODUCTS:

Carbon dioxides, nitrogen oxides, sulfur oxides, halogenated compounds, and hydrogen chloride.

SPECIAL FIRE FIGHTING INSTRUCTIONS:

As in any fire, wear self-contained breathing apparatus and full protective gear.

Section 6: ACCIDENTAL RELEASE MEASURES

General Information:

Use appropriate protective equipment and engineering controls (refer to Section 8).

Specific Information:

Ventilate area. Contain spilled product. For small spills, add suitable absorbent material. Scoop up and place in an appropriate liquid-tight container equipped with a tight cover for disposal. For large spills, dike spilled material or otherwise contain material to ensure runoff does not reach a waterway. Place spilled material in an appropriate, liquid-tight container equipped with a tight cover for disposal. Minimize contact of spilled material with soils to prevent runoff to surface waterways.

Dispose of in accordance with Section 13.

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Section 7: HANDLING AND STORAGE

HANDLING:

Use only in accordance with product literature. Wash thoroughly with warm water and soap after handling.

STORAGE:

Store product at 15-30° (59-86°F). Protect from light.
Shelf Life: Expiration date is listed on each package.

Section 8: EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS:

No special containment is required. Local exhaust ventilation should be provided when handling bulk liquids.

RESPIRATORY PROTECTION:

Not required during normal clinical use.

SKIN PROTECTION:

Not required during normal clinical use. Wash thoroughly with warm water and soap after handling. Impervious gloves are recommended when directly handling bulk liquids.

EYE PROTECTION:

Not required during normal clinical use. Appropriate eye protection is required when handling bulk liquids.

ADDITIONAL PROTECTIVE CLOTHING & EQUIPMENT:

No special recommendations during normal clinical use.

Section 9: PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL PROPERTIES:

Appearance / Physical State: Clear, colorless to nearly colorless. Sterile, isotonic buffered, slightly viscous, aqueous solution
Odor/Threshold Limit: Not Available

CHEMICAL PROPERTIES:

Boiling Point:	Not Available	Melting Point:	Not Available
Vapor Pressure:	Not Available	Vapor Density:	Not Available
Solubility In Water:	Dorzolamide Hydrochloride: Soluble in water (41.1 g/L at 20°C) Slightly soluble in methanol and ethanol	Specific Gravity (H₂O = 1):	1.02 (Water = 1)
	Timolol Maleate: Easily soluble in cold water.	Evaporation Rate:	Not Available
pH:	5.65	Partition Coefficient:	Dorzolamide Hydrochloride: Log Kow: 0.292
		Freezing Point:	Not Available
		Molecular Weight:	Not Available

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Section 10: STABILITY AND REACTIVITY

GENERAL:

Stable

CONDITIONS TO AVOID:

Not available

INCOMPATIBLE MATERIALS:

Dorzolamide Hydrochloride: Strong bases and oxidizing agents. Stainless steel.

Timolol Maleate: None known

HAZARDOUS POLYMERIZATION:

Will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Carbon dioxides, nitrogen oxides, sulfur oxides, halogenated compounds, and hydrogen chloride.

Section 11: TOXICOLOGICAL INFORMATION

RTECS No.: XJ9095163

Dorzolamide Hydrochloride

Toxicity Data: ORL-RAT LD50: 1927 MG/KG

Toxicity Data: ORL-MOUSE LD50: 1320 MG/KG

RTECS No.: UA8475000

Timolol Maleate

Toxicity Data: ORL-RAT LD50: 1028 MG/KG

Toxicity Data: ORL-MOUSE LD50: 1137 MG/KG

RTECS No.: FJ5958000

Hydroxyethyl Cellulose

Toxicity Data: INTRAPERITONEAL-MOUSE TDL₀: 500 MG/KG

RTECS No.: OP2060000

Mannitol

Toxicity Data: ORL-RAT LD50: 13500 MG/KG

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Section 11: TOXICOLOGICAL INFORMATION (cont.)

RTECS No.: BO3150000

Benzalkonium Chloride

Toxicity Data: ORL-RAT LD50: 50-500 MG/KG

NOTE: Only selected Registry of Toxic Effects of Chemical Substances (RTECS) data is presented here. See actual entry in RTECS for complete information.

Refer to Section 3 for additional acute / chronic hazard information.

Section 12: ECOLOGICAL INFORMATION

ENVIRONMENTAL EFFECTS:

Practically non-toxic to aquatic organisms.

Dorzolamide Hydrochloride: Based upon the Activated Sludge Respiration Inhibition Test (ASRIT) EC50 results, concentrations less than 800 mg/L are not expected to upset an un-acclimated activated sludge system in a wastewater treatment plant.

Timolol Maleate: No significant aquatic toxicity has been reported. Based on ASRIT results, concentrations must be >1000 mg/L to inhibit an unacclimated sludge system in a sewage treatment plant.

ECOTOXICITY DATA:

Component	Species	Period	Result
Dorzolamide Hydrochloride	<i>Daphnia magna</i> (LC50)	48 Hours	699 mg/L
	Fathead minnow (LC50)	96 Hours	> 1000 mg/L
Timolol Maleate	<i>Daphnia magna</i> (LC50)	48 Hours	161 mg/L
	<i>Pimephales promelas</i> (LC50)	96 Hours	411 mg/L

ENVIRONMENTAL FATE:

Dorzolamide Hydrochloride: Dorzolamide hydrochloride is not readily biodegradable. However, it is not likely to bioaccumulate or persist since the log Kow = 0.292 and the compound is soluble in water.

Timolol Maleate: Timolol maleate is soluble in water and unlikely to bioaccumulate. The compound is not readily biodegradable and does not hydrolyze. It does, however, photo-degrade slowly.

Section 13: DISPOSAL CONSIDERATIONS

All disposal methods must be in compliance with all Federal, State/Provincial and local laws and regulations. Regulations may vary in different locations. Waste characterizations and compliance with applicable laws are the responsibility solely of the waste generator.

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Section 14: TRANSPORT INFORMATION

	US DOT	IATA	IMO	RID/ADR	Canadian DG
Shipping Name:	Not Regulated	Not Regulated	No Information Available	No Information Available	No Information Available
Hazard Class:	NA	NA			
UN Number:	NA	NA			
Package Group:	NA	NA			

There are no unreasonable risks (health, safety, or property), that this product would pose when transported in commerce. Hazard class definitions (49 CFR, Part 173) are not applicable to this product.

Section 15: REGULATORY INFORMATION

OSHA HAZARD COMMUNICATION STANDARD (29 CFR 1910.1200):

Although technically exempt from the Occupational Safety & Health Administration (OSHA) Hazard Communication Standard, this product would be considered hazardous.

TOXIC SUBSTANCE CONTROL ACT (TSCA):

CAS# 9004-62-0 is listed on the TSCA inventory.

CAS# 69-65-8 is listed on the TSCA inventory.

CAS# 7732-18-5 is listed on the TSCA inventory.

SARA TITLE III (Superfund Amendments and Reauthorization Act):

SECTION 302 (Extremely Hazardous Substances): No Components Listed

SECTION 311, 312 (Hazard Categories): NA

SECTION 313 (Toxic Chemicals): No Components Listed

CALIFORNIA PROPOSITION 65:

This product contains no listed substances known to the State of California to cause cancer, birth defects or other reproductive harm, at levels that would require a warning under the statute.

Section 16: OTHER INFORMATION

To the best of our knowledge, the information contained herein is accurate. However, neither Bausch & Lomb Incorporated nor any of its subsidiaries assumes any liability whatsoever for the accuracy or completeness of the information contained herein. Final determination of suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards that exist. NO WARRANTY, EXPRESS OR IMPLIED, OF MERCHANTABILITY, FITNESS OR OTHERWISE IS MADE. In no event shall Bausch & Lomb Incorporated or any of its subsidiaries be liable for any special, incidental or consequential damages.