SAFETY DATA SHEET
Timolol / Dorzolamide Formulation

Version 3.7  Revision Date: 09/13/2019  SDS Number: 28810-00015  Date of last issue: 24.04.2019  Date of first issue: 06.11.2014

1. PRODUCT AND COMPANY IDENTIFICATION

Product name : Timolol / Dorzolamide Formulation

Manufacturer or supplier’s details
Company : MSD
Address : Briahnager - Off Pune Nagar Road
Wagholi - Pune - India 412 207
Telephone : 908-740-4000
Emergency telephone number : 1-908-423-6000
E-mail address : EHSDATASTEWARD@msd.com
Telefax : 908-735-1496

Recommended use of the chemical and restrictions on use
Recommended use : Pharmaceutical

2. HAZARDS IDENTIFICATION

Manufacture, Storage and Import of Hazardous Chemicals Rules 1989
Classification
Not classified as hazardous according to criteria laid down in Part I of Schedule-1.

GHS Classification
Specific target organ toxicity - repeated exposure : Category 1 (Cardio-vascular system, Central nervous system, Gastrointestinal tract, Lungs)

GHS label elements
Hazard pictograms : ☣️

Signal word : Danger

Hazard statements : H372 Causes damage to organs (Cardio-vascular system, Central nervous system, Gastrointestinal tract, Lungs) through prolonged or repeated exposure.

Precautionary statements : Prevention:
P260 Do not breathe mist or vapours.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.

Response:
3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture : Mixture

<table>
<thead>
<tr>
<th>Components</th>
<th>Chemical name</th>
<th>CAS-No.</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dorzolamide</td>
<td>130693-82-2</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
<tr>
<td></td>
<td>(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-</td>
<td>26921-17-5</td>
<td>&gt;= 0.1 - &lt; 1</td>
</tr>
<tr>
<td></td>
<td>morpholino-1,2,5-thiadiazole monomaleate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. FIRST AID MEASURES

General advice : In the case of accident or if you feel unwell, seek medical advice immediately. When symptoms persist or in all cases of doubt seek medical advice.

If inhaled : If inhaled, remove to fresh air. Get medical attention.

In case of skin contact : In case of contact, immediately flush skin with soap and plenty of water. Remove contaminated clothing and shoes. Get medical attention. Wash clothing before reuse. Thoroughly clean shoes before reuse.

In case of eye contact : Flush eyes with water as a precaution. Get medical attention if irritation develops and persists.

If swallowed : If swallowed, DO NOT induce vomiting. Get medical attention. Rinse mouth thoroughly with water.

Most important symptoms and effects, both acute and delayed : Causes damage to organs through prolonged or repeated exposure.

Protection of first-aiders : First Aid responders should pay attention to self-protection, and use the recommended personal protective equipment when the potential for exposure exists (see section 8).

Notes to physician : Treat symptomatically and supportively.

5. FIREFIGHTING MEASURES

Suitable extinguishing media : Water spray
Alcohol-resistant foam
Carbon dioxide (CO2)
Dry chemical

Unsuitable extinguishing : None known.
media
Specific hazards during fire-fighting
Hazardous combustion products

Specific extinguishing methods
Special protective equipment for firefighters

6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures

Environmental precautions

Methods and materials for containment and cleaning up

7. HANDLING AND STORAGE

Technical measures
Local/Total ventilation
Advice on safe handling
Conditions for safe storage: Keep in properly labelled containers.
Store in accordance with the particular national regulations.

Materials to avoid: Do not store with the following product types:
Strong oxidizing agents

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Components with workplace control parameters

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>Value type (Form of exposure)</th>
<th>Control parameters / Permissible concentration</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorzolamide</td>
<td>130693-82-2</td>
<td>TWA</td>
<td>10 µg/m3 (OEB 3) Internal</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Further information: Eye, Skin

| Wipe limit | 100 µg/100 cm² | Internal |

Engineering measures: Use appropriate engineering controls and manufacturing technologies to control airborne concentrations (e.g., drip-less quick connections). All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment. Containment technologies suitable for controlling compounds are required to control at source and to prevent migration of the compound to uncontrolled areas (e.g., open-face containment devices). Minimize open handling.

Personal protective equipment

Respiratory protection: If adequate local exhaust ventilation is not available or exposure assessment demonstrates exposures outside the recommended guidelines, use respiratory protection.

Filter type: Particulates type

Hand protection: Chemical-resistant gloves

Remarks: Consider double gloving.

Eye protection: Wear safety glasses with side shields or goggles.
If the work environment or activity involves dusty conditions, mists or aerosols, wear the appropriate goggles. Wear a faceshield or other full face protection if there is a potential for direct contact to the face with dusts, mists, or aerosols.
Skin and body protection: Work uniform or laboratory coat. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces. Use appropriate degowning techniques to remove potentially contaminated clothing.

Hygiene measures: If exposure to chemical is likely during typical use, provide eye flushing systems and safety showers close to the working place. When using do not eat, drink or smoke. Wash contaminated clothing before re-use. The effective operation of a facility should include review of engineering controls, proper personal protective equipment, appropriate degowning and decontamination procedures, industrial hygiene monitoring, medical surveillance and the use of administrative controls.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: liquid

Colour: colourless

Odour: No data available

Odour Threshold: No data available

pH: 5.6

Melting point/freezing point: No data available

Initial boiling point and boiling range: No data available

Flash point: No data available

Evaporation rate: No data available

Flammability (solid, gas): Not applicable

Flammability (liquids): No data available

Upper explosion limit / Upper flammability limit: No data available

Lower explosion limit / Lower flammability limit: No data available

Vapour pressure: No data available

Relative vapour density: No data available

Relative density: 1.02

Density: No data available
SAFETY DATA SHEET

Timolol / Dorzolamide Formulation

Solubility(ies)
Water solubility: soluble
Partition coefficient: n-octanol/water: No data available
Auto-ignition temperature: No data available
Decomposition temperature: No data available
Viscosity
Viscosity, kinematic: No data available
Explosive properties: Not explosive
Oxidizing properties: The substance or mixture is not classified as oxidizing.
Molecular weight: No data available
Particle size: No data available

10. STABILITY AND REACTIVITY
Reactivity: Not classified as a reactivity hazard.
Chemical stability: Stable under normal conditions.
Possibility of hazardous reactions: Can react with strong oxidizing agents.
Conditions to avoid: None known.
Incompatible materials: Oxidizing agents
Hazardous decomposition products: No hazardous decomposition products are known.

11. TOXICOLOGICAL INFORMATION
Information on likely routes of exposure:
Inhalation
Skin contact
Ingestion
Eye contact

Acute toxicity
Not classified based on available information.

Product:
Acute oral toxicity: Acute toxicity estimate: > 5,000 mg/kg
Method: Calculation method

Components:
Dorzolamide:
Acute oral toxicity: LD50 (Rat): 1,927 mg/kg
LD50 (Mouse): 1,320 mg/kg
Acute inhalation toxicity: Remarks: No data available
Acute dermal toxicity : Remarks: No data available

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Acute oral toxicity : LD50 (Rat): 1,000 mg/kg
LD50 (Mouse): 1,140 mg/kg
Acute toxicity (other routes of administration) :
LD50 (Mouse): 300 mg/kg
Application Route: Intraperitoneal
LD50 (Mouse): 800 mg/kg
Application Route: Subcutaneous

Skin corrosion/irritation
Not classified based on available information.

Components:
(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Species : Rabbit
Method : Draize Test
Result : No skin irritation

Serious eye damage/eye irritation
Not classified based on available information.

Components:
Dorzolamide:
Species : Monkey
Result : Mild eye irritation

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Species : Rabbit
Result : Mild eye irritation
Species : Dog
Result : No eye irritation

Respiratory or skin sensitisation

Skin sensitisation
Not classified based on available information.

Respiratory sensitisation
Not classified based on available information.

Components:
Dorzolamide:
Test Type : Maximisation Test
Exposure routes : Skin contact
Species: Guinea pig
Result: Weak sensitizer

**Germ cell mutagenicity**
Not classified based on available information.

**Components:**

**Dorzolamide:**
Genotoxicity in vitro:
- Test Type: Chromosomal aberration
  - Result: negative
- Test Type: Alkaline elution assay
  - Test system: rat hepatocytes
  - Result: negative
- Test Type: In vitro mammalian cell gene mutation test
  - Test system: Chinese hamster fibroblasts
  - Result: negative
- Test Type: Bacterial reverse mutation assay (AMES)
  - Result: negative

Genotoxicity in vivo:
- Test Type: Cytogenetic assay
  - Species: Mouse
  - Result: negative

**(S)-3-[3-(tert-buty lamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:**
Genotoxicity in vitro:
- Test Type: Bacterial reverse mutation assay (AMES)
  - Method: OECD Test Guideline 471
  - Result: negative

Genotoxicity in vivo:
- Test Type: In vivo micronucleus test
  - Species: Mouse
  - Method: OECD Test Guideline 474
  - Result: negative

**Carcinogenicity**
Not classified based on available information.

**Components:**

**Dorzolamide:**
Species: Rat, male
Application Route: Oral
Exposure time: 2 Years
- 20 mg/kg body weight
Result: negative
Remarks: The mechanism or mode of action may not be relevant in humans.

Species: Mouse
Application Route: Oral
### (S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>2 Years</td>
</tr>
<tr>
<td>LOAEL</td>
<td>300 mg/kg body weight</td>
</tr>
<tr>
<td>Result</td>
<td>negative</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Adrenal gland</td>
</tr>
<tr>
<td>Remarks</td>
<td>The significance of these findings for humans is not certain.</td>
</tr>
</tbody>
</table>

Species: Mouse, female
Application Route: Oral
Exposure time: 18 Months
LOAEL: 500 mg/kg body weight
Result: negative
Target Organs: Lungs, Mammary gland, Uterus (including cervix)
Remarks: The significance of these findings for humans is not certain.

**Carcinogenicity - Assessment:**
Weight of evidence does not support classification as a carcinogen

**Reproductive toxicity**
Not classified based on available information.

**Components:**

**Dorzolamide:**

**Effects on fertility**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Fertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Rat, male and female</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Fertility NOAEL</td>
<td>7.5 mg/kg body weight</td>
</tr>
<tr>
<td>Result</td>
<td>Animal testing did not show any effects on fertility.</td>
</tr>
</tbody>
</table>

**Effects on foetal development**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Developmental Toxicity NOAEL</td>
<td>1 mg/kg body weight</td>
</tr>
<tr>
<td>Result</td>
<td>Embryotoxic effects and adverse effects on the offspring were detected only at high maternally toxic doses</td>
</tr>
</tbody>
</table>

Test Type: Development
Species: Rabbit
Application Route: Oral
Developmental Toxicity: LOAEL: 2.5 mg/kg body weight
Result: Embryotoxic effects and adverse effects on the offspring were detected only at high maternally toxic doses

**Effects on fertility (S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Fertility/early embryonic development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td></td>
</tr>
<tr>
<td>Application Route</td>
<td></td>
</tr>
<tr>
<td>Developmental Toxicity NOAEL</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td></td>
</tr>
</tbody>
</table>
SAFETY DATA SHEET

Timolol / Dorzolamide Formulation

Species: Rat
Application Route: Oral
Fertility: NOAEL Mating/Fertility: 150 mg/kg body weight
Early Embryonic Development: NOAEL F1: 150 mg/kg body weight

Effects on foetal development:
- Test Type: Embryo-foetal development
- Species: Rabbit
- Developmental Toxicity: LOAEL F1: 50 mg/kg body weight
- Result: Some evidence of adverse effects on development, based on animal experiments.

Reproductive toxicity - Assessment:
- Some evidence of adverse effects on development, based on animal experiments.

STOT - single exposure
Not classified based on available information.

STOT - repeated exposure
Causes damage to organs (Cardio-vascular system, Central nervous system, Gastrointestinal tract, Lungs) through prolonged or repeated exposure.

Product:
- Target Organs: Cardio-vascular system, Central nervous system, Gastrointestinal tract, Lungs
- Assessment: Causes damage to organs through prolonged or repeated exposure.

Components:

Dorzolamide:
- Target Organs: Central nervous system, Gastrointestinal tract, Bone, Blood, Bladder
- Assessment: May cause damage to organs through prolonged or repeated exposure.

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
- Target Organs: Lungs, Cardio-vascular system
- Assessment: Causes damage to organs through prolonged or repeated exposure.

Repeated dose toxicity

Components:

Dorzolamide:
- Species: Rat
- NOAEL: 0.05 mg/kg
- Application Route: Oral
- Target Organs: Bladder, Kidney

Species: Dog
- NOAEL: 0.05 mg/kg
SAFETY DATA SHEET

Timolol / Dorzolamide Formulation

Version: 3.7
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LOAEL: 2 mg/kg
Application Route: Oral
Exposure time: 1 yr
Target Organs: Gastrointestinal tract, Bone, Blood

Species: Monkey
NOAEL: 0.05 mg/kg
Exposure time: 1 yr
Target Organs: Gastrointestinal tract, Bone, Blood

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Species: Rat
NOAEL: 25 mg/kg
Application Route: Oral
Exposure time: 67 Weeks

Species: Dog
NOAEL: 10 mg/kg
Application Route: Oral
Exposure time: 54 Weeks
Target Organs: Kidney

Aspiration toxicity
Not classified based on available information.

Experience with human exposure

Product:
Eye contact
Symptoms: The most common side effects are:, bitter taste, burning or stinging of the eye, Blurred vision, Abdominal pain, Dizziness, digestive disorder, eye pain, Headache, hypertension, Nausea, upper respiratory tract infection

Components:
Dorzolamide:
Eye contact
Symptoms: burning or stinging of the eye, Blurred vision, tearing, asthenia, bitter taste, Nausea, dry mouth, Headache

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Eye contact
Symptoms: burning or stinging of the eye, dryness of the eyes, Headache, Nausea, Dizziness, dry mouth, changes in libido, hair loss, Allergic reactions

Ingestion
Symptoms: Headache, Fatigue, Respiratory disorders, Gastrointestinal discomfort, Allergic reactions, Rash, hair loss, altered mental status, Dizziness, changes in libido

12. ECOLOGICAL INFORMATION

Ecotoxicity

Components:
Dorzolamide:
Toxicity to fish:
- LC50 (Pimephales promelas (fathead minnow)): > 1,000 mg/l
- Exposure time: 96 h

Toxicity to daphnia and other aquatic invertebrates:
- EC50 (Daphnia magna (Water flea)): 699 mg/l
- Exposure time: 48 h

Toxicity to microorganisms:
- EC50 (Natural microorganism): > 800 mg/l
- Exposure time: 3 h
- Test Type: Respiration inhibition
- Method: OECD Test Guideline 209

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:

Toxicity to fish:
- LC50 (Pimephales promelas (fathead minnow)): 411 mg/l
- Exposure time: 96 h

Toxicity to daphnia and other aquatic invertebrates:
- EC50 (Daphnia magna (Water flea)): 161 mg/l
- Exposure time: 48 h
- Method: OECD Test Guideline 202

Toxicity to microorganisms:
- EC50: > 1,000 mg/l
- Exposure time: 3 h
- Test Type: Respiration inhibition
- Method: OECD Test Guideline 209

Persistence and degradability

Components:

Dorzolamide:
- Biodegradability: Result: not rapidly degradable
- Biodegradation: 5 %
- Exposure time: 28 d
- Method: OECD Test Guideline 314

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
- Biodegradability: Result: Not readily biodegradable.
- Biodegradation: 0 %
- Exposure time: 30 d

Stability in water:
- Hydrolysis: 0 % (61 d)
- Method: FDA 3.09

Bioaccumulative potential

Components:

Dorzolamide:
- Partition coefficient: n-octanol/water: log Pow: 0.292

(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Partition coefficient: n-octanol/water : log Pow: 1.48

Mobility in soil
No data available

Other adverse effects
No data available

13. DISPOSAL CONSIDERATIONS

Disposal methods
Waste from residues : Dispose of in accordance with local regulations.
Contaminated packaging : Empty containers should be taken to an approved waste handling site for recycling or disposal.
If not otherwise specified: Dispose of as unused product.

14. TRANSPORT INFORMATION

International Regulations

UNRTDG
Not regulated as a dangerous good

IATA-DGR
Not regulated as a dangerous good

IMDG-Code
Not regulated as a dangerous good

Transport in bulk according to IMO instruments
Not applicable for product as supplied.

15. REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture

The components of this product are reported in the following inventories:
AICS : not determined
DSL : not determined
IECSC : not determined

16. OTHER INFORMATION

Further information
SAFETY DATA SHEET

Timolol / Dorzolamide Formulation

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Full text of other abbreviations

AICS - Australian Inventory of Chemical Substances; ANTT - National Agency for Transport by Land of Brazil; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; ICS0 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50% of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; Nch - Chilean Norm; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NOM - Official Mexican Norm; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative; WHMIS - Workplace Hazardous Materials Information System

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and shall not be considered a warranty or quality specification of any type. The information provided relates only to the specific material identified at the top of this SDS and may not be valid when the SDS material is used in combination with any other materials or in any process, unless specified in the text. Material users should review the information and recommendations in the specific context of their intended manner of handling, use, processing and storage, including an assessment of the appropriateness of the SDS material in the user's end product, if applicable.

IN / EN