SAFETY DATA SHEET

Timolol / Dorzolamide Formulation

Version 3.7  Revision Date: 09/13/2019  SDS Number: 28820-00015  Date of last issue: 24.04.2019  Date of first issue: 06.11.2014

Section 1: Identification

Product name: Timolol / Dorzolamide Formulation

Manufacturer or supplier’s details
Company: MSD
Address: 33 Whakatiki Street - Private Bag 908 Upper Hutt - New Zealand
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

Section 2: Hazard identification

GHS Classification
Specific target organ toxicity - repeated exposure: STOT RE1 (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:
P314 Get medical advice/ attention if you feel unwell.

Disposal:
P501 Dispose of contents/ container to an approved waste disposal plant.
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Other hazards which do not result in classification

None known.

Section 3: Composition/information on ingredients

Substance / Mixture : Mixture

Components

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>CAS-No.</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorzolamide</td>
<td>130693-82-2</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>morpholino-1,2,5-thiadiazole monomaleate</td>
<td>26921-17-5</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Section 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 Protection of first-aiders : Causes damage to organs through prolonged or repeated exposure.
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.

Section 5: Fire-fighting measures

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

Unsuitable extinguishing media : None known.

Specific hazards during firefighting : Exposure to combustion products may be a hazard to health.

Hazardous combustion products : Carbon oxides
Nitrogen oxides (NOx)
Sulphur oxides
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Hydrogen chloride

Specific extinguishing methods:
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.
Use water spray to cool unopened containers.
Remove undamaged containers from fire area if it is safe to do so.
Evacuate area.

Special protective equipment for firefighters:
In the event of fire, wear self-contained breathing apparatus.
Use personal protective equipment.

Section 6: Accidental release measures

Personal precautions, protective equipment and emergency procedures:
Use personal protective equipment.
Follow safe handling advice and personal protective equipment recommendations.

Environmental precautions:
Discharge into the environment must be avoided.
Prevent further leakage or spillage if safe to do so.
Prevent spreading over a wide area (e.g. by containment or oil barriers).
Retain and dispose of contaminated wash water.
Local authorities should be advised if significant spillages cannot be contained.

Methods and materials for containment and cleaning up:
Soak up with inert absorbent material.
For large spills, provide dyking or other appropriate containment to keep material from spreading. If dyked material can be pumped, store recovered material in appropriate container.
Clean up remaining materials from spill with suitable absorbent.
Local or national regulations may apply to releases and disposal of this material, as well as those materials and items employed in the cleanup of releases. You will need to determine which regulations are applicable.
Sections 13 and 15 of this SDS provide information regarding certain local or national requirements.

Section 7: Handling and storage

Technical measures:
See Engineering measures under EXPOSURE CONTROLS/PERSONAL PROTECTION section.

Local/Total ventilation:
Use only with adequate ventilation.

Advice on safe handling:
Avoid inhalation of vapour or mist.
Do not swallow.
Avoid contact with eyes.
Avoid prolonged or repeated contact with skin.
Handle in accordance with good industrial hygiene and safety practice, based on the results of the workplace exposure assessment.
Take care to prevent spills, waste and minimize release to the environment.

Hygiene measures:
If exposure to chemical is likely during typical use, provide eye flushing systems and safety showers close to the working
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

Section 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)</td>
<td>Internal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wipe limit</td>
<td>100 µg/100 cm²</td>
<td>Internal</td>
</tr>
<tr>
<td>(S)-3-[3-(tert-butylamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate</td>
<td>26921-17-5</td>
<td>TWA</td>
<td>10 µg/m³ (OEB 3)</td>
<td>Internal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wipe limit</td>
<td>100 µg/100 cm²</td>
<td>Internal</td>
</tr>
</tbody>
</table>

Engineering measures: Use appropriate engineering controls and manufacturing technologies to control airborne concentrations (e.g., dripless 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

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.

**Section 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
- **Solubility(ies)**:
  - **Water solubility**: soluble
- **Partition coefficient: n-octanol/water**: No data available
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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

Section 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.

Section 11: Toxicological information
Exposure routes
  Inhalation
  Skin contact
  Ingestion
  Eye contact

Acute toxicity
Not classified based on available information.

Product:
  Acute oral toxicity: Acute toxicity estimate: > 2,000 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

**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
Chronic toxicity

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-butylamino)-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
Exposure time : 21 month(s)
Result : negative
(S)-3-[3-(tert-buty lamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:

Species: Rat
Application Route: Oral
Exposure time: 2 Years
LOAEL: 300 mg/kg body weight
Result: negative
Target Organs: Adrenal gland
Remarks: The significance of these findings for humans is not certain.

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: Test Type: Fertility
Species: Rat, male and female
Application Route: Oral
Fertility: NOAEL: 7.5 mg/kg body weight
Result: Animal testing did not show any effects on fertility.

Effects on foetal development: Test Type: Development
Species: Rabbit
Application Route: Oral
Developmental Toxicity: NOAEL: 1 mg/kg body weight
Result: Embryotoxic effects and adverse effects on the offspring were detected only at high maternally toxic doses

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

(S)-3-[3-(tert-buty lamino)-2-hydroxypropoxy]-4-morpholino-1,2,5-thiadiazole monomaleate:
Effects on fertility: Test Type: Fertility/early embryonic development
Species: Rat
Application Route: Oral
Fertility: NOAEL Mating/Fertility: 150 mg/kg body weight
Early Embryonic Development: NOAEL F1: 150 mg/kg body
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
**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

Section 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: EC50 (Daphnia magna (Water flea)): 699 mg/l
aquatic invertebrates

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-buty lamino)-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

EC50 (Photobacterium phosphoreum): > 1,800 mg/l

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-buty lamino)-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-buty lamino)-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

Section 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.

Section 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 Annex II of MARPOL 73/78 and the IBC Code
Not applicable for product as supplied.

National Regulations
NZS 5433
Not regulated as a dangerous good

Section 15: Regulatory information

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

HSNO Approval Number
HSR100425 Pharmaceutical Active Ingredients Group Standard 2017

HSW Controls
Certified handler certificate not required.
Tracking hazardous substance not required.
Refer to the Health and Safety at Work (Hazardous Substances) Regulations 2017, for further information.

The components of this product are reported in the following inventories:
AICS: not determined
DSL: not determined
IECSC: not determined
Section 16: Other information

Further information

Date format: dd.mm/yyyy

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; IC50 - 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.

NZ / EN