SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

Version 4.3  Revision Date: 23.03.2020  SDS Number: 42693-00014  Date of last issue: 13.09.2019  Date of first issue: 05.01.2015

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier

Trade name : Amiloride / Hydrochlorothiazide Formulation

1.2 Relevant identified uses of the substance or mixture and uses advised against

Use of the Substance/Mixture : Pharmaceutical

1.3 Details of the supplier of the safety data sheet

Company : MSD
117 16th Road
07033 Halfway house, Midrand, South Africa

Telephone : +27 11 655 3000
Telefax : 908-735-1496

E-mail address of person responsible for the SDS : EHSDATASTEWARD@msd.com

1.4 Emergency telephone number

1-908-423-6000

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Classification (REGULATION (EC) No 1272/2008)

Specific target organ toxicity - repeated exposure, Category 1

H372: Causes damage to organs through prolonged or repeated exposure.

2.2 Label elements

Labelling (REGULATION (EC) No 1272/2008)

Hazard pictograms :

Signal word : Danger

Hazard statements : H372 Causes damage to organs through prolonged or repeated exposure.

Precautionary statements :

Prevention:
P260 Do not breathe dust.
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.

Hazardous components which must be listed on the label:
hydrochlorothiazide

2.3 Other hazards
Dust contact with the eyes can lead to mechanical irritation.
Contact with dust can cause mechanical irritation or drying of the skin.
May form explosive dust-air mixture during processing, handling or other means.

SECTION 3: Composition/information on ingredients

3.2 Mixtures

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>EC-No.</th>
<th>Index-No.</th>
<th>Classification</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrochlorothiazide</td>
<td>58-93-5</td>
<td>200-403-3</td>
<td></td>
<td>STOT RE1; H372</td>
<td>&gt;= 20 - &lt; 30</td>
</tr>
<tr>
<td>Amiloride</td>
<td>17440-83-4</td>
<td></td>
<td></td>
<td>Acute Tox.2; H300 Eye Irrit.2; H319 Aquatic Chronic3; H412</td>
<td>&gt;= 1 - &lt; 2,5</td>
</tr>
</tbody>
</table>

For explanation of abbreviations see section 16.

SECTION 4: First aid measures

4.1 Description of 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.

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).

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

In case of skin contact: In case of contact, immediately flush skin with soap and plenty of water.
Get medical attention if symptoms occur.

In case of eye contact: If in eyes, rinse well with water.
Get medical attention if irritation develops and persists.

If swallowed: If swallowed, DO NOT induce vomiting unless directed to do so by medical personnel.
Get medical attention.
Rinse mouth thoroughly with water.
Never give anything by mouth to an unconscious person.

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

Contact with dust can cause mechanical irritation or drying of the skin.
Dust contact with the eyes can lead to mechanical irritation.

4.3 Indication of any immediate medical attention and special treatment needed
Treatment : Treat symptomatically and supportively.

SECTION 5: Firefighting measures

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

Unsuitable extinguishing media : None known.

5.2 Special hazards arising from the substance or mixture
Specific hazards during firefighting : Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Exposure to combustion products may be a hazard to health.

Hazardous combustion products : Carbon oxides
Nitrogen oxides (NOx)
Chlorine compounds
Sulphur oxides
Metal oxides
Oxides of phosphorus

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

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.
SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

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

6.2 Environmental precautions

Environmental precautions: Discharge into the environment must be avoided. Prevent further leakage or spillage if safe to do so. Retain and dispose of contaminated wash water. Local authorities should be advised if significant spillages cannot be contained.

6.3 Methods and material for containment and cleaning up

Methods for cleaning up: Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air). Dust deposits should not be allowed to accumulate on surfaces, as these may form an explosive mixture if they are released into the atmosphere in sufficient concentration. 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.

6.4 Reference to other sections

See sections: 7, 8, 11, 12 and 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Technical measures: Static electricity may accumulate and ignite suspended dust causing an explosion. Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres.

Local/Total ventilation: Use only with adequate ventilation.

Advice on safe handling: Do not breathe dust. 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. Minimize dust generation and accumulation. Keep container closed when not in use. Keep away from heat and sources of ignition. Take precautionary measures against static discharges.
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.

7.2 Conditions for safe storage, including any incompatibilities
Requirements for storage areas and containers:
Keep in properly labelled containers. Store in accordance with the particular national regulations.

Advice on common storage:
Do not store with the following product types:
- Strong oxidizing agents
- Organic peroxides
- Explosives
- Gases

7.3 Specific end use(s)
Specific use(s):
No data available

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Occupational Exposure Limits

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>Value type (Form of exposure)</th>
<th>Control parameters</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrochlorothiazide</td>
<td>58-93-5</td>
<td>TWA</td>
<td>100 µg/m3 (OEB 2)</td>
<td>Internal</td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>TWA OEL-RL (Respirable dust)</td>
<td>5 mg/m3</td>
<td>ZA OEL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Further information: Recommended Limit
|                     |         | TWA OEL-RL (inhalable dust)   | 10 mg/m3                  | ZA OEL      |
| Amiloride           | 17440-83-4 | TWA                           | 100 µg/m3                 | Internal    |

8.2 Exposure controls

Engineering measures
Use feasible engineering controls to minimize exposure to compound. All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment.

Personal protective equipment
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.

Hand protection
Material: Chemical-resistant gloves

Skin and body protection: Work uniform or laboratory coat.

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 (P)

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

Appearance: powder
Colour: pale red-brown
Odour: odourless
Odour Threshold: No data available
pH: No data available
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): May form explosive dust-air mixture during processing, handling or other means.
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: No data available
Density: No data available
Solubility(ies)
Water solubility: No data available
Partition coefficient: n-octanol/water: No data available
Auto-ignition temperature: No data available
Decomposition temperature: No data available
Viscosity
  Viscosity, dynamic : No data available
  Viscosity, kinematic : No data available

Explosive properties : Not explosive
Oxidizing properties : The substance or mixture is not classified as oxidizing.

9.2 Other information
  Flammability (liquids) : No data available
  Molecular weight : 302.10 g/mol
  Particle size : No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
  Not classified as a reactivity hazard.

10.2 Chemical stability
  Stable under normal conditions.

10.3 Possibility of hazardous reactions
  Hazardous reactions : May form explosive dust-air mixture during processing, handling or other means. Can react with strong oxidizing agents.

10.4 Conditions to avoid
  Conditions to avoid : Heat, flames and sparks. Avoid dust formation.

10.5 Incompatible materials
  Materials to avoid : Oxidizing agents

10.6 Hazardous decomposition products
  No hazardous decomposition products are known.

SECTION 11: Toxicological information

11.1 Information on toxicological effects
  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: > 2.000 mg/kg
Method: Calculation method

Components:

hydrochlorothiazide:
Acute oral toxicity
LD50 (Rat): > 2.750 mg/kg
LD50 (Mouse): > 2.830 mg/kg

Acute toxicity (other routes of administration)
LD50 (Rat): 990 mg/kg
Application Route: Intravenous
LD50 (Mouse): 590 mg/kg
Application Route: Intravenous

Amiloride:
Acute oral toxicity
LD50 (Mouse): 56 mg/kg
LD50 (Rat): > 150 mg/kg

Skin corrosion/irritation
Not classified based on available information.

Components:

hydrochlorothiazide:
Species
Rabbit
Result
No skin irritation

Amiloride:
Species
Rabbit
Result
Mild skin irritation
Remarks
slight irritation

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

Components:

hydrochlorothiazide:
Species
Rabbit
Result
Mild eye irritation

Amiloride:
Species
Rabbit
Remarks
Severe eye irritation
Respiratory or skin sensitisation

Skin sensitisation
Not classified based on available information.

Respiratory sensitisation
Not classified based on available information.

Germ cell mutagenicity
Not classified based on available information.

Components:

**hydrochlorothiazide:**
Genotoxicity in vitro:
- Test Type: Bacterial reverse mutation assay (AMES)
  - Result: negative
- Test Type: Chromosomal aberration
  - Test system: Chinese hamster ovary cells
  - Result: negative
- Test Type: sister chromatid exchange assay
  - Test system: Chinese hamster ovary cells
  - Result: positive
- Test Type: in vitro assay
  - Test system: mouse lymphoma cells
  - Result: positive

Genotoxicity in vivo:
- Test Type: Chromosomal aberration
  - Species: Chinese hamster
  - Cell type: Bone marrow
  - Result: negative
- Test Type: in vivo assay
  - Species: Mouse
  - Cell type: Bone marrow
  - Result: negative

Germ cell mutagenicity- Assessment:
Weight of evidence does not support classification as a germ cell mutagen.

**Amiloride:**
Genotoxicity in vitro:
- Test Type: Bacterial reverse mutation assay (AMES)
  - Result: negative

Carcinogenicity
Not classified based on available information.

Components:

**hydrochlorothiazide:**
Species: Mouse, female
Application Route: Oral
Exposure time: 2 Years
Result : negative
Species : Mouse, male
Application Route : Oral
Exposure time : 2 Years
Result : equivocal

Species : Rat, male and female
Application Route : Oral
Exposure time : 2 Years
Result : negative

**Amiloride:**
Species : Rat
Application Route : Oral
Exposure time : 92 weeks
: 10 mg/kg bw/day
Result : negative

Species : Mouse
Application Route : Oral
Exposure time : 104 weeks
: 8 mg/kg bw/day
Result : negative

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

**Components:**
**hydrochlorothiazide:**
Effects on fertility : Test Type: Fertility
Species: Rat, male and female
Application Route: oral (feed)
Fertility: NOAEL: 4 mg/kg body weight
Result: Effects on fertility

Test Type: Fertility
Species: Mouse, male and female
Application Route: oral (feed)
Fertility: NOAEL: 100 mg/kg body weight
Result: Effects on fertility

Effects on foetal development : Test Type: Development
Species: Mouse
Application Route: Oral
Developmental Toxicity: NOAEL: 3.000 mg/kg body weight
Result: No teratogenic effects

Test Type: Development
Species: Rat
Application Route: Oral
Developmental Toxicity: NOAEL: 1.000 mg/kg body weight
Result: No teratogenic effects
Amiloride:
Effects on foetal development: Test Type: Embryo-foetal development
Species: Rabbit
Application Route: Oral
Result: No effects on fertility and early embryonic development were detected.

Test Type: Embryo-foetal development
Species: Mouse
Application Route: Oral
Result: No effects on fertility and early embryonic development were detected.

STOT - single exposure
Not classified based on available information.

STOT - repeated exposure
Causes damage to organs through prolonged or repeated exposure.

Components:

hydrochlorothiazide:
Target Organs: Kidney, Parathyroid gland
Assessment: Causes damage to organs through prolonged or repeated exposure.

Repeated dose toxicity

Components:

hydrochlorothiazide:
Species: Rat, male and female
LOAEL: 10 mg/kg
Application Route: Oral
Exposure time: 2 yr
Target Organs: Kidney, Parathyroid gland

Species: Mouse, male and female
NOAEL: 300 - 550 mg/kg
Application Route: Oral
Exposure time: 2 yr
Remarks: No significant adverse effects were reported

Species: Dog
Application Route: Oral
Exposure time: 9 Months
Target Organs: Parathyroid gland

Aspiration toxicity
Not classified based on available information.
SAFETY DATA SHEET
Amiloride / Hydrochlorothiazide Formulation

Components:
hydrochlorothiazide:
No aspiration toxicity classification

Experience with human exposure

Components:
hydrochlorothiazide:
Eye contact: Symptoms: Eye irritation
Ingestion: Symptoms: Dizziness, Headache, Fatigue, Nausea, Abdominal pain, hypotension, dry mouth, electrolyte imbalance, eye pain

Amiloride:
Ingestion: Symptoms: hyperkalemia

SECTION 12: Ecological information

12.1 Toxicty

Components:
hydrochlorothiazide:
Toxicity to fish: LC50 (Pimephales promelas (fathead minnow)): > 500 mg/l
Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): > 500 mg/l

Amiloride:
Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): 56.3 mg/l

12.2 Persistence and degradability

Components:
hydrochlorothiazide:
Stability in water: Hydrolysis: 46.2 %(96 h)

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
Not relevant
SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

Version 4.3
Revision Date: 23.03.2020
SDS Number: 42693-00014
Date of last issue: 13.09.2019
Date of first issue: 05.01.2015

12.6 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods
Product: Dispose of in accordance with local regulations. According to the European Waste Catalogue, Waste Codes are not product specific, but application specific. Waste codes should be assigned by the user, preferably in discussion with the waste disposal authorities.
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

14.1 UN number
Not regulated as a dangerous good
14.2 UN proper shipping name
Not regulated as a dangerous good
14.3 Transport hazard class(es)
Not regulated as a dangerous good
14.4 Packing group
Not regulated as a dangerous good
14.5 Environmental hazards
Not regulated as a dangerous good
14.6 Special precautions for user
Not applicable
14.7 Transport in bulk according to Annex II of Marpol and the IBC Code
Remarks: Not applicable for product as supplied.

SECTION 15: Regulatory information

15.1 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

15.2 Chemical safety assessment
A Chemical Safety Assessment has not been carried out.
SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

SECTION 16: Other information

Other information: Items where changes have been made to the previous version are highlighted in the body of this document by two vertical lines.

Full text of H-Statements

H300: Fatal if swallowed.
H319: Causes serious eye irritation.
H372: Causes damage to organs through prolonged or repeated exposure.
H412: Harmful to aquatic life with long lasting effects.

Full text of other abbreviations

Acute Tox.: Acute toxicity
Aquatic Chronic: Long-term (chronic) aquatic hazard
Eye Irrit.: Eye irritation
STOT RE: Specific target organ toxicity - repeated exposure
ZA OEL: South Africa. Hazardous Chemical Substances Regulations, Occupational Exposure Limits
ZA OEL / TWA OEL-RL: Long term occupational exposure limits - recommended limit

ADN - European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways; ADR - European Agreement concerning the International Carriage of Dangerous Goods by Road; AICS - Australian Inventory of Chemical Substances; ASTM - American Society for the Testing of Materials; bw - Body weight; CLP - Classification Labelling Packaging Regulation; Regulation (EC) No 1272/2008; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECHA - European Chemicals Agency; EC-Number - European Community number; 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; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Civil Aviation Organization; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; 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; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; 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; RID - Regulations concerning the International Carriage of Dangerous Goods by Rail; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; SVHC - Substance of very high concern; TCSI - Taiwan Chemical Substance Inventory; 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
Further information

Classification of the mixture: STOT RE 1 Classification procedure: Calculation method

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.

ZA / EN