SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

SECTION 1. IDENTIFICATION

Product name: Amiloride / Hydrochlorothiazide Formulation
Other means of identification: No data available

Manufacturer or supplier’s details
Company name of supplier: Merck & Co., Inc
Address: 2000 Galloping Hill Road
Kenilworth - New Jersey - U.S.A. 07033
Telephone: 908-740-4000
Telefax: 908-735-1496
Emergency telephone: 1-908-423-6000
E-mail address: EHSDATASTEWARD@merck.com

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

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with the Hazardous Products Regulations
Acute toxicity (Oral): Category 4
Specific target organ toxicity - repeated exposure: Category 1 (Kidney, Parathyroid gland)

GHS label elements
Hazard pictograms:
Signal Word: Danger
Hazard Statements: H302 Harmful if swallowed.
H372 Causes damage to organs (Kidney, Parathyroid gland) 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:
P301 + P312 + P330 IF SWALLOWED: Call a POISON CENTER/ doctor if you feel unwell. Rinse mouth.
P314 Get medical advice/ attention if you feel unwell.

Disposal:
P501 Dispose of contents/ container to an approved waste disposal plant.
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

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>Hydrochlorothiazide</td>
<td>58-93-5</td>
<td>&gt;= 10 - &lt; 30</td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 10 - &lt; 30</td>
</tr>
<tr>
<td>Amiloride</td>
<td>17440-83-4</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
</tbody>
</table>

Actual concentration or concentration range is withheld as a trade secret

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 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.

Most important symptoms and effects, both acute and delayed : Harmful if swallowed. 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.

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.

SECTION 5. FIRE-FIGHTING MEASURES

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

Unsuitable extinguishing media : None known.
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Specific hazards during fire fighting:
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
- Sulfur oxides
- Metal oxides
- Oxides of phosphorus

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 fire-fighters:
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. 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:
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.

SECTION 7. HANDLING AND STORAGE

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.
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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.
- Take care to prevent spills, waste and minimize release to the environment.

Conditions for safe storage:
- Keep in properly labeled containers.
- Store in accordance with the particular national regulations.

Materials to avoid:
- Do not store with the following product types:
  - Strong oxidizing agents
  - Organic peroxides
  - Explosives
  - Gases

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Ingredients 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>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</td>
<td>10 mg/m³</td>
<td>CA AB OEL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TWA (Total dust)</td>
<td>10 mg/m³</td>
<td>CA QC OEL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TWA (respirable dust fraction)</td>
<td>3 mg/m³</td>
<td>CA BC OEL</td>
</tr>
<tr>
<td>Amiloride</td>
<td>17440-83-4</td>
<td>TWA</td>
<td>100 µg/m³</td>
<td>ACGIH</td>
</tr>
</tbody>
</table>

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

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:
- Material: Chemical-resistant gloves

Date of last issue: 09/13/2019
Date of first issue: 01/05/2015
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.

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.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: powder
Color: pale red-brown
Odor: odorless

Odor 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.

Flammability (liquids): No data available
Upper explosion limit / Upper flammability limit: No data available
Lower explosion limit / Lower flammability limit: No data available
Vapor pressure: No data available
Relative vapor density: No data available
### SECTION 10. STABILITY AND REACTIVITY

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivity</td>
<td>Not classified as a reactivity hazard.</td>
</tr>
<tr>
<td>Chemical stability</td>
<td>Stable under normal conditions.</td>
</tr>
<tr>
<td>Possibility of hazardous reactions</td>
<td>May form explosive dust-air mixture during processing, handling or other means. Can react with strong oxidizing agents.</td>
</tr>
<tr>
<td>Conditions to avoid</td>
<td>Heat, flames and sparks.</td>
</tr>
<tr>
<td></td>
<td>Avoid dust formation.</td>
</tr>
<tr>
<td>Incompatible materials</td>
<td>Oxidizing agents</td>
</tr>
<tr>
<td>Hazardous decomposition products</td>
<td>No hazardous decomposition products are known.</td>
</tr>
</tbody>
</table>

### SECTION 11. TOXICOLOGICAL INFORMATION

**Information on likely routes of exposure**
- Inhalation
- Skin contact
- Ingestion
- Eye contact

**Acute toxicity**
- Harmful if swallowed.

**Product:**
- Acute oral toxicity: Acute toxicity estimate: 1,785 mg/kg
## Components:

### Hydrochlorothiazide:

<table>
<thead>
<tr>
<th>Component</th>
<th>Acute oral toxicity</th>
<th>Application Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>LD50 (Rat): &gt; 2,750 mg/kg</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>LD50 (Mouse): &gt; 2,830 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

### Starch:

<table>
<thead>
<tr>
<th>Component</th>
<th>Acute oral toxicity</th>
<th>Application Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>LD50 (Rat): &gt; 5,000 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

### Amiloride:

<table>
<thead>
<tr>
<th>Component</th>
<th>Acute oral toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>LD50 (Mouse): 56 mg/kg</td>
</tr>
<tr>
<td></td>
<td>LD50 (Rat): &gt; 150 mg/kg</td>
</tr>
</tbody>
</table>

### Skin corrosion/irritation

- Not classified based on available information.

<table>
<thead>
<tr>
<th>Component</th>
<th>Species</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Rabbit</td>
<td>No skin irritation</td>
</tr>
</tbody>
</table>

### Serious eye damage/eye irritation

- Not classified based on available information.

<table>
<thead>
<tr>
<th>Component</th>
<th>Species</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Rabbit</td>
<td>Mild eye irritation</td>
</tr>
<tr>
<td>Starch</td>
<td>Rabbit</td>
<td>No eye irritation</td>
</tr>
</tbody>
</table>
Amiloride:

<table>
<thead>
<tr>
<th>Species</th>
<th>Rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remarks</td>
<td>Severe eye irritation</td>
</tr>
</tbody>
</table>

Respiratory or skin sensitization

**Skin sensitization**
- Not classified based on available information.

**Respiratory sensitization**
- Not classified based on available information.

**Components:**

**Starch:**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Maximization Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routes of exposure</td>
<td>Skin contact</td>
</tr>
<tr>
<td>Species</td>
<td>Guinea pig</td>
</tr>
<tr>
<td>Result</td>
<td>negative</td>
</tr>
</tbody>
</table>

**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 test
  - 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.
Starch:
Genotoxicity in vitro: Test Type: Bacterial reverse mutation assay (AMES), Result: negative

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

Test Type: Embryo-fetal 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 (Kidney, Parathyroid gland) through prolonged or repeated exposure.

Components:

Hydrochlorothiazide:

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

Repeated dose toxicity

Components:

Hydrochlorothiazide:

Species:
LOAEL:
Rat, male and female
10 mg/kg
### Application Route
- Oral

### Exposure time
- 2 y

### Target Organs
- Kidney, Parathyroid gland

### Species
- Mouse, male and female

### NOAEL
- 300 - 550 mg/kg

### Application Route
- Oral

### Exposure time
- 2 y

### Remarks
- No significant adverse effects were reported

### Species
- Dog

### Application Route
- Oral

### Exposure time
- 9 Months

### Target Organs
- Parathyroid gland

### Starch:
- Species: Rat
- NOAEL: >= 2,000 mg/kg
- Application Route: Skin contact
- Exposure time: 28 Days
- Method: OECD Test Guideline 410

### Aspiration toxicity
- Not classified based on available information.

### 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

#### Ecotoxicity

### Components:
- **Hydrochlorothiazide:**
  - **Toxicity to fish**
    - LC50 (Pimephales promelas (fathead minnow)): > 500 mg/l
    - Exposure time: 96 h
Toxicity to daphnia and other aquatic invertebrates:
- Amiloride: EC50 (Daphnia magna (Water flea)): 56.3 mg/l
  Exposure time: 48 h
  Method: OECD Test Guideline 202
- Amiloride: EC50 (Daphnia magna (Water flea)): > 500 mg/l
  Exposure time: 48 h

Persistence and degradability
Components:
- Hydrochlorothiazide:
  Stability in water: Hydrolysis: 46.2 % (96 h)

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.

Transport Information
- 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.
- Domestic regulator:
- TDG: Not regulated as a dangerous good
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SECTION 15. REGULATORY INFORMATION

The ingredients of this product are reported in the following inventories:

AICS : not determined
DSL : not determined
IECSC : not determined

SECTION 16. OTHER INFORMATION

Full text of other abbreviations

ACGIH : USA. ACGIH Threshold Limit Values (TLV)
CA BC OEL : Canada. British Columbia OEL
CA QC OEL : Québec. Regulation respecting occupational health and safety, Schedule 1, Part 1: Permissible exposure values for airborne contaminants
ACGIH / TWA : 8-hour, time-weighted average
CA AB OEL / TWA : 8-hour Occupational exposure limit
CA BC OEL / TWA : 8-hour time weighted average
CA QC OEL / TWAEV : Time-weighted average exposure value

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 Na-
SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

Version: 6.0
Revision Date: 03/23/2020
SDS Number: 42677-00014
Date of last issue: 09/13/2019
Date of first issue: 01/05/2015


Sources of key data used to compile the Material Safety Data Sheet:

Revision Date: 03/23/2020

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

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.

CA / Z8