SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Amiloride / Hydrochlorothiazide Formulation

Manufacturer or supplier's details

Company: MSD

Address: Avenida Tanner de Melo, Quadra 10 Lote 4A, Galpão A Parque Industrial Vice Presidente José Alencar Aparecida de Goias – GO, Brazil

Telephone: 908-740-4000

Emergency telephone: 1-908-423-6000

E-mail address: EHSDATASTEWARD@msd.com

Recommended use of the chemical and restrictions on use

Recommended use: Pharmaceutical

SECTION 2. HAZARDS IDENTIFICATION

GHS Classification in accordance with ABNT NBR 14725 Standard

Acute toxicity (Oral): Category 4

Specific target organ toxicity - repeated exposure: Category 1 (Kidney, Parathyroid gland)

GHS label elements in accordance with ABNT NBR 14725 Standard

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.
Other hazards which do not result in classification
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

<table>
<thead>
<tr>
<th>Substance / Mixture</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance / Mixture</td>
<td>Mixture</td>
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<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;= 20 -&lt; 30</td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 10 -&lt; 20</td>
</tr>
<tr>
<td>Amiloride</td>
<td>17440-83-4</td>
<td>&gt;= 1 -&lt; 2,5</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 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 : Harmful if swallowed.
and effects, both acute and delayed
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.

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 (see section 7) and personal protective equipment recommendations (see section 8).

Environmental precautions
Avoid release to the environment.
Prevent further leakage or spillage if safe to do so.
Retain and dispose of contaminated wash water.
Local authorities should be advised if significant spills 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).
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.

Advice on safe handling: Do not breathe dust. Do not swallow. Avoid contact with eyes. Avoid prolonged or repeated contact with skin. Wash skin thoroughly after handling. 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. Do not eat, drink or smoke when using this product. 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 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.

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
Components | CAS-No. | Value type (Form of exposure) | Control parameters / Permissible concentration | Basis |
---|---|---|---|---|
Hydrochlorothiazide | 58-93-5 | TWA | 100 µg/m³ (OEB 2) | Internal |
Starch | 9005-25-8 | TWA | 10 mg/m³ | ACGIH |
Amiloride | 17440-83-4 | TWA | 100 µg/m³ | Internal |

**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

**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.

### 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
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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
Relative density : No data available
Density : No data available
Solubility(ies)
  Water solubility : No data available
Partition coefficient: n-octanol/water : No data available
Autoignition 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.
Molecular weight : 302,10 g/mol
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
  May form explosive dust-air mixture during processing, handling or other means.
  Can react with strong oxidizing agents.
Conditions to avoid : Heat, flames and sparks.
Incompatible materials
  Avoid dust formation.
  Oxidizing agents
Hazardous decomposition products : No hazardous decomposition products are known.

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
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

**Starch:**
- Acute oral toxicity: LD50 (Rat): > 5.000 mg/kg

- Acute dermal toxicity: LD50 (Rabbit): > 2.000 mg/kg

**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

Starch:
Species: Rabbit
Result: No eye irritation

Amiloride:
Species: Rabbit
Remarks: Severe eye irritation

Respiratory or skin sensitization
Skin sensitization
Not classified based on available information.

Respiratory sensitization
Not classified based on available information.

Components:

Starch:
Test Type: Maximization Test
Routes of exposure: Skin contact
Species: Guinea pig
Result: negative

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
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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
Result : negative

Species : Mouse
Application Route : Oral
Exposure time : 104 weeks
Result : negative

Species : Mouse
Application Route : Oral
Exposure time : 104 weeks
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: 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 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: EC50 (Daphnia magna (Water flea)): > 500 mg/l
  Exposure time: 48 h

Amiloride:
- Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): 56,3 mg/l
  Exposure time: 48 h
  Method: OECD Test Guideline 202

Persistence and degradability

Components:

Hydrochlorothiazide:
- Stability in water: Hydrolysis: 46,2 % (96 h)

Bioaccumulative potential
No data available

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
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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 regulation

ANTT
Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture
National List of Carcinogenic Agents for Humans - (LINACH)
Group 2B: Possibly carcinogenic to humans
Hydrochlorothiazide 58-93-5

Brazil. List of chemicals controlled by the Federal Police: Not applicable

International Regulations

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

SECTION 16. OTHER INFORMATION

Further information

Full text of other abbreviations
ACGIH : USA. ACGIH Threshold Limit Values (TLV)
ACGIH / TWA : 8-hour, time-weighted average

AIIC - Australian Inventory of Industrial Chemicals; 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
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