SAFETY DATA SHEET

Amiloride / Hydrochlorothiazide Formulation

1. PRODUCT AND COMPANY IDENTIFICATION

Chemical product name : Amiloride / Hydrochlorothiazide Formulation

Supplier’s company name, address and phone number
Company name of supplier : MSD
Address : Kumagaya, Saitama Prefecture , Xicheng 810 MSD Co., Ltd. Menuma factory
Telephone : 048-588-8411
E-mail address : EHSDATASTEWARD@msd.com
Emergency telephone number : +1-908-423-6000

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

2. HAZARDS IDENTIFICATION

GHS classification of chemical product
Specific target organ toxicity - repeated exposure : Category 1 (Kidney, Parathyroid gland)

GHS label elements
Hazard pictograms : 

Signal word : Danger

Hazard statements : 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:
P314 Get medical advice/ attention if you feel unwell.

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

Other hazards which do not result in classification
Important symptoms and out- : Dust contact with the eyes can lead to mechanical irritation.
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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>
<th>ENCS No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>58-93-5</td>
<td>&gt;= 20 - &lt; 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 10 - &lt; 20</td>
<td>8-98</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>17440-83-4</td>
<td>&gt;= 1 - &lt; 2.5</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 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 : 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.

5. FIREFIGHTING 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 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.

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.

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

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). 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.

7. HANDLING AND STORAGE

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.
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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.

Avoidance of contact:
Hygiene measures: Oxidizing agents
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.

Storage
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

Packaging material: Unsuitable material: None known.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Threshold limit value and permissible exposure limits for each component in the work environment

<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>ACGIH</td>
</tr>
<tr>
<td>Amiloride</td>
<td>17440-83-4</td>
<td>TWA</td>
<td>100 µg/m³</td>
<td>Internal</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

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.

9. PHYSICAL AND CHEMICAL PROPERTIES

Physical state : powder

Colour : pale red-brown

Odour : odourless

Odour Threshold : No data available

Melting point/freezing point : No data available

Boiling point, initial boiling point and boiling range : No data available

Flammability (solid, gas) : May form explosive dust-air mixture during processing, handling or other means.

Flammability (liquids) : No data available

Lower explosion limit and upper explosion limit / flammability limit

Upper explosion limit / Upper flammability limit : No data available

Lower explosion limit / Lower flammability limit : No data available

Flash point : No data available

Decomposition temperature : No data available

pH : No data available

Evaporation rate : No data available

Auto-ignition temperature : No data available

Viscosity

Viscosity, dynamic : No data available
Viscosity, kinematic: No data available

Solubility(ies)
Water solubility: No data available

Partition coefficient: n-octanol/water: No data available

Vapour pressure: No data available

Density and/or relative density
Relative density: No data available

Density: No data available

Relative vapour density: 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 characteristics
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
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.
Avoid dust formation.

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: > 2,000 mg/kg
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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 sensitisation

Skin sensitisation  
Not classified based on available information.

Respiratory sensitisation  
Not classified based on available information.

Components:

Starch:

Test Type: Maximisation Test  
Exposure routes: 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 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.
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:

<table>
<thead>
<tr>
<th>Species</th>
<th>Mouse, female</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>Result</td>
<td>negative</td>
</tr>
</tbody>
</table>

Species
Application Route: Oral
Exposure time: 2 Years
Result: equivocal

Species
Application Route: Oral
Exposure time: 2 Years
Result: negative

Amiloride:
Species: Rat
Application Route: Oral
Exposure time: 92 weeks
Result: negative

Species
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 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 (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
<table>
<thead>
<tr>
<th>Application Route</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure time</td>
<td>2 yr</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Kidney, Parathyroid gland</td>
</tr>
<tr>
<td>Species</td>
<td>Mouse, male and female</td>
</tr>
<tr>
<td>NOAEL</td>
<td>300 - 550 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>2 yr</td>
</tr>
<tr>
<td>Remarks</td>
<td>No significant adverse effects were reported</td>
</tr>
<tr>
<td>Species</td>
<td>Dog</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>9 Months</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Parathyroid gland</td>
</tr>
</tbody>
</table>

**Starch:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>&gt;= 2,000 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Skin contact</td>
</tr>
<tr>
<td>Exposure time</td>
<td>28 Days</td>
</tr>
<tr>
<td>Method</td>
<td>OECD Test Guideline 410</td>
</tr>
</tbody>
</table>

**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

**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

Hazardous to the ozone layer
Not applicable

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 Annex II of MARPOL 73/78 and the IBC Code
Not applicable for product as supplied.
National Regulations
Refer to section 15 for specific national regulation.

15. REGULATORY INFORMATION

Related Regulations

Fire Service Law
Not applicable to dangerous materials / designated flammables.

Chemical Substance Control Law
Not applicable for Specified Chemical Substance, Monitoring Chemical Substance and Priority Assessment Chemical Substance.

Industrial Safety and Health Law

Harmful Substances Prohibited from Manufacture
Not applicable

Harmful Substances Required Permission for Manufacture
Not applicable

Substances Prevented From Impairment of Health
Not applicable

Circular concerning Information on Chemicals having Mutagenicity - Annex 2: Information on Existing Chemicals having Mutagenicity
Not applicable

Circular concerning Information on Chemicals having Mutagenicity - Annex 1: Information on Notified Substances having Mutagenicity
Not applicable

Substances Subject to be Notified Names
Not applicable

Substances Subject to be Indicated Names
Not applicable

Ordinance on Prevention of Hazards Due to Specified Chemical Substances
Not applicable

Ordinance on Prevention of Lead Poisoning
Not applicable

Ordinance on Prevention of Tetraalkyl Lead Poisoning
Not applicable

Ordinance on Prevention of Organic Solvent Poisoning
Not applicable

Enforcement Order of the Industrial Safety and Health Law - Attached table 1 (Dangerous Substances)
Not applicable

Poisonous and Deleterious Substances Control Law
Not applicable
Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof
Not applicable

High Pressure Gas Safety Act
Not applicable

Explosive Control Law
Not applicable

Vessel Safety Law
Not regulated as a dangerous good

Aviation Law
Not regulated as a dangerous good

Marine Pollution and Sea Disaster Prevention etc Law
Bulk transportation : Not classified as noxious liquid substance
Pack transportation : Not classified as marine pollutant

Narcotics and Psychotropics Control Act
Narcotic or Psychotropic Raw Material (Export / Import Permission)
Not applicable

Specific Narcotic or Psychotropic Raw Material (Export / Import permission)
Not applicable

Waste Disposal and Public Cleansing Law
Industrial waste

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

Date format : yyyy/mm/dd

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
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.