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
              Shotton Lane
              NE23 3JU Cramlington NU - Great Britain
   Telephone : 44 1 670 59 30 00
   Telefax : 908-735-1496
   E-mail address of person responsible for the SDS : EHSDATASETWARD@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.
Amiloride / Hydrochlorothiazide Formulation

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>Registration number</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></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></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. 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.

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

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
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. Equipment should conform to NS EN 143

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
Amiloride / Hydrochlorothiazide Formulation

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.
Amiloride / Hydrochlorothiazide Formulation

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
Amiloride / Hydrochlorothiazide Formulation

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
: 50 - 200 mg/kg
Amiloride / Hydrochlorothiazide Formulation

**Application Route**: Oral

**Exposure time**: 9 Months

**Target Organs**: Parathyroid gland

**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**

**12.1 Toxicity**

**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

**12.2 Persistence and degradability**

**Components**:

- **hydrochlorothiazide**:
  - **Stability in water**: Hydrolysis: 46.2 % (96 h)
Amiloride / Hydrochlorothiazide Formulation

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

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
REACH - Restrictions on the manufacture, placing on the market and use of certain dangerous substances, preparations and articles (Annex XVII): Not applicable
SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006

Amiloride / Hydrochlorothiazide Formulation

Version 4.3  Revision Date: 23.03.2020  SDS Number: 44154-00014  Date of last issue: 13.09.2019
Date of first issue: 05.01.2015

REACH - Candidate List of Substances of Very High Concern for Authorisation (Article 59).
REACH - List of substances subject to authorisation (Annex XIV)
Regulation (EC) No 1005/2009 on substances that deplete the ozone layer
Regulation (EU) 2019/1021 on persistent organic pollutants (recast)
Regulation (EC) No 649/2012 of the European Parliament and the Council concerning the export and import of dangerous chemicals
Not applicable

Other regulations:
Young people under the age of 18 are not allowed to use or be exposed to the product professionally. Young people above the age of 15 are, however, except from this rule if the product is a necessary part of their education.

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.

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

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
Amiloride / Hydrochlorothiazide Formulation

Further information
Sources of key data used to compile the Safety Data Sheet

Classification of the mixture:
STOT RE 1 H372

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.

NO / EN