SAFETY DATA SHEET

Lisinopril / Hydrochlorothiazide Formulation

Version 2
Revision Date: 10.10.2020
SDS Number: 4573754-00008
Date of last issue: 13.04.2020
Date of first issue: 08.07.2019

SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Lisinopril / 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
Reproductive toxicity: Category 1A
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: H360D May damage the unborn child.
H372 Causes damage to organs (Kidney, Parathyroid gland) through prolonged or repeated exposure.

Precautionary Statements:
Prevention:
P201 Obtain special instructions before use.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P280 Wear protective gloves/ protective clothing/ eye protection/ face protection.
Response:
P308 + P313 IF exposed or concerned: Get medical advice/ attention.
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Storage:
P405 Store locked up.

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 combustible dust concentrations in air 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>Classification</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>Acute toxicity (Oral), Category 5 Specific target organ toxicity - repeated exposure (Kidney, Parathyroid gland), Category 1</td>
<td>&gt;= 10 &lt; 20</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>58-93-5</td>
<td>Acute toxicity (Oral), Category 5 Specific target organ toxicity - repeated exposure (Kidney, Parathyroid gland), Category 1</td>
<td>&gt;= 10 &lt; 20</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>83915-83-7</td>
<td>Reproductive toxicity, Category 1A Specific target organ toxicity - repeated exposure (Oral) (Kidney), Category 2</td>
<td>&gt;= 5 &lt; 10</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.

In case of skin contact: In case of contact, immediately flush skin with soap and plenty of water.
Remove contaminated clothing and shoes.
Get medical attention.
Wash clothing before reuse.
Thoroughly clean shoes before reuse.

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.
Get medical attention.
Rinse mouth thoroughly with water.

Most important symptoms and effects, both acute and: May damage the unborn child.
Causes damage to organs through prolonged or repeated
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:
- 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 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: If sufficient ventilation is unavailable, use with local exhaust ventilation.

Advice on safe handling: Do not get on skin or clothing. Do not breathe dust, fume, gas, mist, vapors or spray. Do not swallow. Avoid contact with eyes. Wash skin thoroughly after handling. Handle in accordance with good industrial hygiene and safety practice, based on the results of the workplace exposure assessment. Keep container tightly closed. 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 locked up. Keep tightly closed. 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
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Components | CAS-No. | Value type (Form of exposure) | Control parameters / Permissible concentration | Basis
-------------|---------|-------------------------------|-----------------------------------------------|-------
Starch      | 9005-25-8 | TWA             | 10 mg/m³ | ACGIH
Hydrochlorothiazide | 58-93-5 | TWA               | 100 µg/m³ (OEB 2) | Internal
Lisinopril  | 83915-83-7 | TWA             | 20 µg/m³ (OEB 3) | 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**: solid

**Color**: No data available

**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**: Not applicable

**Evaporation rate**: Not applicable

**Flammability (solid, gas)**: May form combustible dust concentrations in air during processing, handling or other means.
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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 : Not applicable
Relative vapor density : Not applicable
Relative density : No data available
Density : No data available
Solubility(ies)
  Water solubility : No data available
Partition coefficient: n-octanol/water : Not applicable
Autoignition temperature : No data available
Decomposition temperature : No data available
Viscosity
  Viscosity, kinematic : Not applicable
Explosive properties : Not explosive
Oxidizing properties : The substance or mixture is not classified as oxidizing.
Molecular weight : No data available
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 combustible dust concentrations in air 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.

SECTION 11. TOXICOLOGICAL INFORMATION

Information on likely routes of : Inhalation
exposure
Skin contact
Ingestion
Eye contact

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

**Product:**
**Acute oral toxicity:**
Acute toxicity estimate: > 5.000 mg/kg
Method: Calculation method

**Components:**
**Starch:**
Acute oral toxicity: LD50 (Rat): > 5.000 mg/kg
Acute dermal toxicity: LD50 (Rabbit): > 2.000 mg/kg

**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

**Lisinopril:**
Acute oral toxicity: LD50 (Rat): > 20.000 mg/kg
LD50 (Mouse): > 20.000 mg/kg

**Skin corrosion/irritation**
Not classified based on available information.

**Components:**
**Hydrochlorothiazide:**
Species: Rabbit
Result: No skin irritation

**Lisinopril:**
Species: Rabbit
Result: Mild skin irritation

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

Starch:
Species: Rabbit
Result: No eye irritation

Hydrochlorothiazide:
Species: Rabbit
Result: Mild eye irritation

Lisinopril:
Species: Rabbit
Result: Mild 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

Lisinopril:
Test Type: Maximization Test
Routes of exposure: Dermal
Result: negative

Germ cell mutagenicity
Not classified based on available information.

Components:

Starch:
Genotoxicity in vitro: Test Type: Bacterial reverse mutation assay (AMES)
Result: negative

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:
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.

Lisinopril:
Genotoxicity in vitro:
Test Type: Bacterial reverse mutation assay (AMES)
Result: negative

Test Type: In vitro mammalian cell gene mutation test
Test system: Chinese hamster lung cells
Result: negative

Test Type: Alkaline elution assay
Test system: rat hepatocytes
Result: negative

Genotoxicity in vivo:
Test Type: Micronucleus test
Species: Mouse
Application Route: Oral
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
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Species: Rat, male and female
Application Route: Oral
Exposure time: 2 Years
Result: negative

Lisinopril:
Species: Rat
Application Route: Oral
Exposure time: 105 weeks
NOAEL: 90 mg/kg body weight
Result: negative

Species: Mouse
Application Route: Oral
Exposure time: 92 weeks
NOAEL: 135 mg/kg body weight
Result: negative

Reproductive toxicity
May damage the unborn child.

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.

Lisinopril:
Effects on fertility: Test Type: Fertility
Species: Rat
Application Route: Oral
Fertility: NOAEL: 300 mg/kg body weight
Symptoms: No effects on mating performance.
Result: Animal testing did not show any effects on fertility.

**Effects on fetal development**
- Test Type: Development
  - Species: Rat
  - Application Route: Oral
  - Developmental Toxicity: LOAEL: 30 mg/kg body weight
  - Result: positive, No teratogenic effects.

- Test Type: Development
  - Species: Mouse
  - Application Route: Oral
  - Developmental Toxicity: LOAEL: 100 mg/kg body weight
  - Symptoms: Total Resorptions / resorption rate.
  - Result: Embryotoxic effects and adverse effects on the offspring were detected.

- Test Type: Development
  - Species: Rabbit
  - Application Route: Oral
  - Developmental Toxicity: LOAEL: 0,1 mg/kg body weight
  - Result: Embryotoxic effects and adverse effects on the offspring were detected.

**Reproductive toxicity - Assessment**
- Positive evidence of adverse effects on development from human epidemiological studies.

**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.

**Lisinopril:**
- Routes of exposure
  - Ingestion
- Target Organs
  - Kidney
- Assessment
  - May cause damage to organs through prolonged or repeated exposure.

**Repeated dose toxicity**

**Components:**

**Starch:**
- Species: Rat
- NOAEL: >= 2.000 mg/kg
- Application Route: Skin contact
Exposure time: 28 Days
Method: OECD Test Guideline 410

**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

**Lisinopril:**
- **Species:** Rat
- **LOAEL:** < 3.650 mg/kg
- **Application Route:** Oral
- **Exposure time:** 1 y
- **Target Organs:** Kidney

- **Species:** Dog
- **LOAEL:** < 840 mg/kg
- **Application Route:** Oral
- **Exposure time:** 4 Weeks
- **Target Organs:** Kidney

**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
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Lisinopril:
Ingestion:
Symptoms: Dizziness, Headache, Fatigue, Diarrhea, Nausea, Cough, Lowered blood pressure, electrolyte imbalance
Remarks: May damage the unborn child.

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

Lisinopril:
Toxicity to daphnia and other aquatic invertebrates:
EC50 (Daphnia magna (Water flea)): 20.000 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
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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 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
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.

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