SAFETY DATA SHEET

Enalapril / Hydrochlorothiazide Formulation

Version: 4.7
Revision Date: 10.10.2020
SDS Number: 402466-00013
Date of last issue: 23.03.2020
Date of first issue: 07.01.2016

SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Enalapril / Hydrochlorothiazide Formulation

Manufacturer or supplier’s details
Company: MSD
Address: 26 Talavera Road, Talavera Corp Centre, Macquarie Park
New South Wales, 2113 Australia
Telephone: (61)-02-8988-8000
Emergency telephone number: (61)-02-8988-8000
E-mail address: EHSDATASTEWARD@msd.com
Telefax: 908-735-1496

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

SECTION 2. HAZARDS IDENTIFICATION

GHS Classification
Reproductive toxicity: Category 1A
Specific target organ toxicity - repeated exposure: Category 1 (Kidney, Parathyroid gland)
Specific target organ toxicity - repeated exposure: Category 2 (Cardio-vascular system)

GHS label elements
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.
H373 May cause damage to organs (Cardio-vascular system) through prolonged or repeated exposure.

Precautionary statements: Prevention:
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P260 Do not breathe dust.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P281 Use personal protective equipment as required.

Response:
P308 + P313 IF exposed or concerned: Get medical advice/attention.

Storage:
P405 Store locked up.

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

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>Mixture</td>
<td></td>
</tr>
</tbody>
</table>

<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>(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate</td>
<td>76095-16-4</td>
<td>&gt;= 1 - &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 delayed:
May damage the unborn child.
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. FIREFIGHTING MEASURES

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

Unsuitable extinguishing media: None known.

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

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 firefighters: 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. 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.

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 labelled 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

SECTION 8. EXPOSURE CONTROLSPERSONAL PROTECTION

Components with workplace control parameters

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>Value type (Form of)</th>
<th>Control parameters / Permissible</th>
<th>Basis</th>
</tr>
</thead>
</table>

4 / 16
SAFETY DATA SHEET
Enalapril / Hydrochlorothiazide Formulation

58-93-5

Hydrochlorothiazide

TWA

100 µg/m³ (OEB 2)

58-93-5

Starch

TWA

10 mg/m³

Further information: This value is for inhalable dust containing no asbestos and < 1% crystalline silica

9005-25-8

Hydrochlorothiazide

TWA

10 mg/m³

9005-25-8

Hydrochlorothiazide

TWA

10 mg/m³

Further information: This value is for inhalable dust containing no asbestos and < 1% crystalline silica

76095-16-4

Further information: This value is for inhalable dust containing no asbestos and < 1% crystalline silica

500 µg/100 cm²

Wipe limit

Further information: This value is for inhalable dust containing no asbestos and < 1% crystalline silica

Engineering measures
All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment.
Containment technologies suitable for controlling compounds are required to control at source and to prevent migration of the compound to uncontrolled areas (e.g., open-face containment devices).
Minimize open handling.

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
Chemical-resistant gloves

Remarks
Consider double gloving.

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 face shield 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.
Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces.
Use appropriate degowning techniques to remove potentially contaminated clothing.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES
Appearance
powder

Colour
No data available

Odour
No data available

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 : Not applicable
Evaporation rate : Not applicable
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
Vapour pressure : No data available
Relative vapour 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
Auto-ignition 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.
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 reac- : May form explosive dust-air mixture during processing, han-
SECTION 11. TOXICOLOGICAL INFORMATION

**Exposure routes:** 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

**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

**(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:**
Acute oral toxicity: LD50 (Rat): 2,000 - 3,500 mg/kg
LDLo (Rat): 1,775 mg/kg
LD50 (Mouse): 2,000 - 3,500 mg/kg
LDLo (Mouse): 1,000 mg/kg

Acute toxicity (other routes of administration): LD50 (Rat): 850 mg/kg
Application Route: Intravenous
LD50 (Mouse): 750 mg/kg
Application Route: Intravenous

LD50 (Dog): > 100 mg/kg
LDLo (Dog): 200 mg/kg

Skin corrosion/irritation
Not classified based on available information.

**Components:**

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

**(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:**
Species : Rabbit
Result : No skin 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

**(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:**
Species : Rabbit
Result : Severe 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
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(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:

Test Type: Maximisation Test
Exposure routes: Skin contact
Species: Guinea pig
Result: Not a skin sensitizer.

Chronic toxicity

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

(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:

Genotoxicity in vitro:
- Test Type: Bacterial reverse mutation assay (AMES)
  Result: negative
  Test Type: In vitro sister chromatid exchange assay in mammalian cells
  Result: negative
Test Type: Alkaline elution assay  
Result: negative

Genotoxicity in vivo  
Species: Mouse  
Application Route: Ingestion  
Result: negative

Test Type: Mammalian erythrocyte micronucleus test (in vivo cytogenetic assay)  
Species: Mouse  
Application Route: Ingestion  
Result: negative

Test Type: Mutagenicity (in vivo mammalian bone-marrow cytogenetic test, chromosomal analysis)  
Species: Mouse  
Application Route: Ingestion  
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

(S)-1-\{N-\{Ethoxycarbonyl\}-3-phenylpropyl\}-L-alanyl-L-proline maleate:
Species: Rat  
Application Route: Ingestion  
Exposure time: 106 weeks  
NOAEL: 90 mg/kg body weight  
Result: negative

Species: Mouse  
Application Route: Ingestion  
Exposure time: 94 weeks  
NOAEL: 90 - 180 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 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

(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:

Effects on fertility:
- Test Type: Fertility
  - Species: Rat, male and female
  - Application Route: Ingestion
  - Fertility: NOAEL: 90 mg/kg body weight
  - Result: No effects on fertility

Effects on foetal development:
- Species: Rat
  - Application Route: Ingestion
  - Developmental Toxicity: NOAEL: 200 mg/kg body weight
  - Result: No effects on foetal development

  - Species: Rat
    - Application Route: Ingestion
    - Developmental Toxicity: LOAEL: 1,200 mg/kg body weight
    - Result: Fetotoxicity

  - Species: Rat
    - Application Route: Ingestion
    - Developmental Toxicity: LOAEL: 30 mg/kg body weight
    - Result: Effects on postnatal development, Effects on newborn, No teratogenic effects

  - Species: Rabbit
    - Application Route: Ingestion
    - General Toxicity Maternal: LOAEL: 1 mg/kg body weight
    - Developmental Toxicity: LOAEL: 1 mg/kg body weight
Result: Fetotoxicity, Maternal toxicity observed, No teratogenic effects

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. May cause damage to organs (Cardio-vascular system) through prolonged or repeated exposure.

**Components:**

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

**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
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

(S)-1-[N-[(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:

Species: Dog
NOAEL: 15 mg/kg
LOAEL: 30 mg/kg
Application Route: Ingestion
Exposure time: 1 yr
Target Organs: Kidney

Species: Rat
NOAEL: 90 mg/kg
Application Route: Oral
Exposure time: 1 yr
Remarks: No significant adverse effects were reported

Species: Monkey
NOAEL: 30 mg/kg
Application Route: Oral
Exposure time: 1 Months
Remarks: No significant adverse effects were reported

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

(S)-1-[N-[(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:
Ingestion: Target Organs: Cardio-vascular system
Symptoms: hypotension, Cough, Dizziness, Headache, Blurred vision, Fatigue, Oedema, Nausea, hyperkalemia, fainting, Weakness, skin rash
Remarks: May cause harm to 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

(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:

Toxicity to fish
- LC50 (Pimephales promelas (fathead minnow)): > 1,000 mg/l
  Exposure time: 96 h
  Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates
- EC50 (Daphnia magna (Water flea)): 346 mg/l
  Exposure time: 48 h
  Method: OECD Test Guideline 202

Toxicity to microorganisms
- EC50 (Natural microorganism): > 1,000 mg/l
  Exposure time: 3 h
  Test Type: Respiration inhibition
  Method: OECD Test Guideline 209

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
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
ADG
Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture

Prohibition/Licensing Requirements : There is no applicable prohibition, authorisation and restricted use requirements, including for carcinogens referred to in Schedule 10 of the model WHS Act and Regulations.

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

SECTION 16. OTHER INFORMATION

Further information
Revision Date : 10.10.2020
Date format : dd.mm.yyyy

Full text of other abbreviations
ACGIH : USA. ACGIH Threshold Limit Values (TLV)
AU OEL : Australia. Workplace Exposure Standards for Airborne Contaminants.
ACGIH / TWA : 8-hour, time-weighted average
AU OEL / TWA : Exposure standard - 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
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