Section 1: Identification

Product name: Enalapril / Hydrochlorothiazide Formulation

Manufacturer or supplier’s details

Company: MSD
Address: 33 Whakatiki Street - Private Bag 908
        Upper Hutt - New Zealand
Telephone: 908-740-4000
Emergency telephone number: 1-908-423-6000
E-mail address: EHSDATASTEWARD@msd.com
Telefax: 908-735-1496

Recommended use of the chemical and restrictions on use

Recommended use: Pharmaceutical

Section 2: Hazard identification

GHS Classification

Reproductive toxicity: Repr.1A
Specific target organ toxicity - repeated exposure: STOT RE1 (Kidney, Parathyroid gland)
Specific target organ toxicity - repeated exposure: STOT RE2 (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.
Section 3: Composition/information on ingredients

<table>
<thead>
<tr>
<th>Substance / Mixture</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemical name</td>
</tr>
<tr>
<td>Mixture</td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td></td>
<td>Starch</td>
</tr>
<tr>
<td></td>
<td>(S)-1-[N-{1-(Ethoxycarbonyl)-3-phenylpropyl}-L-alanyl]-L-proline maleate</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: Fire-fighting 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 and personal protective equipment recommendations.

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.

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.
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.
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 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 controls/personal protection

Components with workplace control parameters

<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>
</table>

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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 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. 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 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.

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
Method: Calculation method

Components:
Hydrochlorothiazide:
Acute oral toxicity: LD50 (Rat): 10,000 mg/kg
LD50 (Mouse): 10,000 mg/kg
Acute toxicity (other routes of administration):
LD50 (Rat): 990 mg/kg
Application Route: Intravenous
LD50 (Dog): 250 mg/kg
Application Route: Intravenous

Starch:
Acute oral toxicity: LD50 (Mouse): > 5,000 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

**(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:**

**(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
Enalapril / Hydrochlorothiazide Formulation

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:

Genotoxicity in vitro:

Germ cell mutagenicity - Assessment:

Weight of evidence does not support classification as a germ cell mutagen.

(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:

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-[1-(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.
(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate:
Target Organs: Kidney, Cardio-vascular system
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
Application Route: Oral
Exposure time: 9 Months
Target Organs: Parathyroid gland

(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-[1-(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

NZS 5433
Not regulated as a dangerous good

Section 15: Regulatory information

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

HSNO Approval Number
HSR100425 Pharmaceutical Active Ingredients Group Standard 2017

HSW Controls
Certified handler certificate not required.
Tracking hazardous substance not required.
Refer to the Health and Safety at Work (Hazardous Substances) Regulations 2017, for further information.
The components of this product are reported in the following inventories:

<table>
<thead>
<tr>
<th>Inventory</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>AICS</td>
<td>not determined</td>
</tr>
<tr>
<td>DSL</td>
<td>not determined</td>
</tr>
<tr>
<td>IECSC</td>
<td>not determined</td>
</tr>
</tbody>
</table>

Section 16: Other information

Further information

Sources of key data used to compile the Safety Data Sheet:
- Date format: dd.mm.yyyy

Full text of other abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACGIH</td>
<td>USA. ACGIH Threshold Limit Values (TLV)</td>
</tr>
<tr>
<td>NZ OEL</td>
<td>New Zealand. Workplace Exposure Standards for Atmospheric Contaminants</td>
</tr>
<tr>
<td>ACGIH / TWA</td>
<td>8-hour, time-weighted average</td>
</tr>
<tr>
<td>NZ OEL / WES-TWA</td>
<td>Workplace Exposure Standard - Time Weighted average</td>
</tr>
</tbody>
</table>

Acronyms:
- AICS - Australian Inventory of Chemical Substances; 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 Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemicals in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardisation; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50% of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; Nch - Chilean Norm; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NOM - Official Mexican Norm; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods;
vPvB - Very Persistent and Very Bioaccumulative; WHMIS - Workplace Hazardous Materials Information System

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.

NZ / EN