SAFETY DATA SHEET

BUTORPHANOL FORMULATION

Version 2.0  Revision Date: 2020/03/23  SDS Number: 918665-00009  Date of last issue: 2019/09/13
Date of first issue: 2016/10/03

1. PRODUCT AND COMPANY IDENTIFICATION

Chemical product name: Butorphanol Formulation

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: Veterinary product

2. HAZARDS IDENTIFICATION

GHS classification of chemical product
Specific target organ toxicity - single exposure (Oral): Category 2 (Central nervous system)
Specific target organ toxicity - repeated exposure (Oral): Category 2 (Blood, Central nervous system)

GHS label elements
Hazard pictograms:
Signal word: Warning
Hazard statements: H371 May cause damage to organs (Central nervous system) if swallowed.
H373 May cause damage to organs (Blood, Central nervous system) through prolonged or repeated exposure if swallowed.

Precautionary statements
Prevention:
P260 Do not breathe mist or vapours.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
Response:
P308 + P311 IF exposed or concerned: Call a POISON CENTER/ doctor.
Storage:
SAFETY DATA SHEET
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P405 Store locked up.

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

Other hazards which do not result in classification
None known.

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>[17-((Cyclobutylmethyl)morphinan-3,14-diyl [S-(R*,R*)]-2,3-dihydroxysuccinate</td>
<td>58786-99-5</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.

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 : Flush eyes with water as a precaution.
Get medical attention if irritation develops and persists.

If swallowed : If swallowed, DO NOT induce vomiting.
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 : May cause damage to organs if swallowed.
May cause damage to organs through prolonged or repeated exposure if swallowed.

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
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Unsuitable extinguishing media: None known.
Specific hazards during firefighting:
- Exposure to combustion products may be a hazard to health.
Hazardous combustion products:
- Carbon 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.

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.
- Prevent spreading over a wide area (e.g. by containment or oil barriers).
- 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:
- Soak up with inert absorbent material.
- For large spills, provide dyking or other appropriate containment to keep material from spreading. If dyked material can be pumped, store recovered material in appropriate container.
- Clean up remaining materials from spill with suitable absorbent.
- 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:
- See Engineering measures under EXPOSURE CONTROLS/PERSONAL PROTECTION section.
Local/Total ventilation:
- Use only with adequate ventilation.
Advice on safe handling:
- Avoid inhalation of vapour or mist.
- Do not swallow.
- Avoid contact with eyes.
- Avoid prolonged or repeated contact with skin.
- Handle in accordance with good industrial hygiene and safety...
Avoidance of contact: Oxidizing agents

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.

Storage
Conditions for safe storage: Keep in properly labelled containers. Store locked up. 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</th>
<th>Control parameters / Permissible concentration</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-((Cyclobutylmethyl)morphinan-3,14-diyl [S-(R*,R*)]-2,3-dihydroxysuccinate</td>
<td>58786-99-5</td>
<td>TWA</td>
<td>3 µg/m³ (OEB 4)</td>
<td>Internal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wipe limit</td>
<td>30 µg/100 cm²</td>
</tr>
</tbody>
</table>

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. Essentially no open handling permitted. Use closed processing systems or containment technologies. If handled in a laboratory, use a properly designed biosafety cabinet, fume hood, or other containment device if the potential exists for aerosolization. If this potential does not exist, handle over lined trays or benchtops.

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
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.

9. PHYSICAL AND CHEMICAL PROPERTIES

- **Physical state**: liquid
- **Colour**: colourless
- **Odour**: No data available
- **Odour Threshold**: No data available
- **Melting point/freezing point**: No data available
- **Boiling point, initial boiling point and boiling range**: 100 °C
- **Flammability (solid, gas)**: Not applicable
- **Flammability (liquids)**: No data available
- **Lower explosion limit and upper explosion limit / flammability limit**: No data available
- **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**: No data available
- **Viscosity, kinematic**: No data available
10. STABILITY AND REACTIVITY

Reactivity: Not classified as a reactivity hazard.
Chemical stability: Stable under normal conditions.
Possibility of hazardous reactions: Can react with strong oxidizing agents.
Conditions to avoid: None known.
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
  Method: Calculation method

Components:
- 17-(Cyclobutylmethyl)morphinan-3,14-diyl [S-(R*,R*)]-2,3-dihydroxysuccinate:
  Acute oral toxicity: LD50 (Mouse): 395 mg/kg
LD50 (Dog): > 50 mg/kg
LD50 (Monkey): > 50 mg/kg

Acute inhalation toxicity : Remarks: No data available
Acute dermal toxicity : Remarks: No data available

Skin corrosion/irritation
Not classified based on available information.

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyi [S-(R*,R*)]-2,3-dihydroxysuccinate:
Remarks : No data available

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

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyi [S-(R*,R*)]-2,3-dihydroxysuccinate:
Species : Rat
Result : No eye irritation

Respiratory or skin sensitisation

Skin sensitisation
Not classified based on available information.

Respiratory sensitisation
Not classified based on available information.

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyi [S-(R*,R*)]-2,3-dihydroxysuccinate:
Exposure routes : Dermal
Assessment : Does not cause skin sensitisation.
Result : negative

Germ cell mutagenicity
Not classified based on available information.

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyi [S-(R*,R*)]-2,3-dihydroxysuccinate:
Genotoxicity in vitro : Test Type: Bacterial reverse mutation assay (AMES)
Result: negative

Test Type: DNA damage and repair, unscheduled DNA synthesis in mammalian cells (in vitro)
Result: negative
Carcinogenicity
Not classified based on available information.

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyl [S-(R*,R*)]-2,3-dihydroxysuccinate:
Species: Rat
Application Route: Oral
Exposure time: 2 Years
Result: negative

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

Reproductive toxicity
Not classified based on available information.

Components:
17-(Cyclobutylmethyl)morphinan-3,14-diyl [S-(R*,R*)]-2,3-dihydroxysuccinate:
Effects on fertility: Test Type: Fertility/early embryonic development
Species: Rat
Application Route: Oral
Fertility: LOAEL: 160 mg/kg body weight
Result: Effects on fertility

Effects on foetal development: Test Type: Embryo-foetal development
Species: Rat
Application Route: Subcutaneous
Developmental Toxicity: LOAEL: 1 mg/kg body weight
Result: No teratogenic effects, Increased stillbirths

Species: Rabbit
Application Route: Oral
Developmental Toxicity: LOAEL: 30 mg/kg body weight
Result: No teratogenic effects, Maternal toxicity observed., Postimplantation loss.

Species: Rat
Application Route: Subcutaneous
Developmental Toxicity: LOAEL: 0.5 mg/kg body weight
Result: Maternal toxicity observed.

Reproductive toxicity - Assessment: Some evidence of adverse effects on sexual function and fertility, based on animal experiments., Some evidence of adverse effects on development, based on animal experiments.

STOT - single exposure
May cause damage to organs (Central nervous system) if swallowed.
Components:

17-(Cyclobutylmethyl)morphinan-3,14-diy| [S-(R*,R*)]-2,3-dihydroxysuccinate:
- Target Organs: Central nervous system
- Assessment: Causes damage to organs.

STOT - repeated exposure
May cause damage to organs (Blood, Central nervous system) through prolonged or repeated exposure if swallowed.

Components:

17-(Cyclobutylmethyl)morphinan-3,14-diy| [S-(R*,R*)]-2,3-dihydroxysuccinate:
- Target Organs: Blood, Central nervous system
- Assessment: Causes damage to organs through prolonged or repeated exposure.

Repeated dose toxicity

Components:

17-(Cyclobutylmethyl)morphinan-3,14-diy| [S-(R*,R*)]-2,3-dihydroxysuccinate:
- Species: Rat
  - LOAEL: 0.4 mg/kg
  - Application Route: Subcutaneous
  - Exposure time: 6 Months
  - Target Organs: Blood, Central nervous system

- Species: Monkey
  - LOAEL: 0.15 mg/kg
  - Application Route: Intramuscular
  - Exposure time: 6 Months
  - Target Organs: Central nervous system

- Species: Dog
  - LOAEL: 0.1 mg/kg
  - Application Route: Intramuscular
  - Exposure time: 3 Months
  - Symptoms: reduced body weight gain

Aspiration toxicity
Not classified based on available information.

Experience with human exposure

Components:

17-(Cyclobutylmethyl)morphinan-3,14-diy| [S-(R*,R*)]-2,3-dihydroxysuccinate:
- Ingestion: Symptoms: Drowsiness, Sweating, Nausea, Dizziness, Vertigo, Palpitation, respiratory depression
12. ECOLOGICAL INFORMATION

Ecotoxicity

**Components:**

17-(Cyclobutylmethyl)morphinan-3,14-diyld [S-(R*,R*)]-2,3-dihydroxysuccinate:

Toxicity to daphnia and other aquatic invertebrates:

EC50 (Daphnia magna (Water flea)): 38.1 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

Persistence and degradability
No data available

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
12. OTHER INFORMATION

Further information

Items where changes have been made to the previous version are highlighted in the body of this document by two vertical lines.

Date format: yyyy/mm/dd

Full text of other abbreviations

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
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JP / EN