SAFETY DATA SHEET
Imipenem / Cilastatin Formulation

SECTION 1. IDENTIFICATION

Product name : Imipenem / Cilastatin Formulation
Other means of identification : No data available

Manufacturer or supplier’s details
Company name of supplier : Merck & Co., Inc
Address : 2000 Galloping Hill Road
Kenilworth - New Jersey - U.S.A. 07033
Telephone : 908-740-4000
Emergency telephone : 1-908-423-6000
E-mail address : EHSDATASTEWARD@merck.com

Recommended use of the chemical and restrictions on use
Recommended use : Pharmaceutical
Restrictions on use : Not applicable

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with the Hazardous Products Regulations
Eye irritation : Category 2A
Respiratory sensitization : Sub-category 1A
Reproductive toxicity : Category 2

GHS label elements
Hazard pictograms : 

Signal Word : Danger
Hazard Statements : H319 Causes serious eye irritation.
H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H361d Suspected of damaging the unborn child.

Precautionary Statements
Prevention:
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P261 Avoid breathing dust.
P264 Wash skin thoroughly after handling.
P280 Wear protective gloves, protective clothing, eye protection and face protection.
P284 Wear respiratory protection.

Response:
P304 + P340 IF INHALED: Remove person to fresh air and keep comfortable for breathing.
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308 + P313 IF exposed or concerned: Get medical attention.
P337 + P313 If eye irritation persists: Get medical attention.

Storage:
P405 Store locked up.

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

Other hazards
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>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components</strong></td>
<td></td>
</tr>
<tr>
<td>Chemical name</td>
<td>Common Name/Synonym</td>
</tr>
<tr>
<td>Cilastatin</td>
<td>No data available</td>
</tr>
<tr>
<td>Imipenem</td>
<td>No data available</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. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. 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: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If easy to do, remove contact lens, if worn. Get medical attention.

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:
Causes serious eye irritation.
May cause allergy or asthma symptoms or breathing difficulties if inhaled.
Suspected of damaging the unborn child.
Excessive exposure may aggravate preexisting asthma and other respiratory disorders (e.g. emphysema, bronchitis, reactive airways dysfunction syndrome).
Contact with dust can cause mechanical irritation or drying of the skin.

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 fire fighting:
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

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: Use only with adequate ventilation.

Advice on safe handling: Avoid breathing dust.
Do not swallow.
Do not get in eyes.
Avoid prolonged or repeated contact with skin.
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.
Already sensitized individuals should consult their physician regarding working with respiratory irritants or sensitizers.
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.

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

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Ingredients 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>
<tbody>
<tr>
<td>Cilastatin</td>
<td>81129-83-1</td>
<td>TWA</td>
<td>5 mg/m3 (OEB 1)</td>
<td>Internal</td>
</tr>
<tr>
<td>Imipenem</td>
<td>74431-23-5</td>
<td>TWA</td>
<td>1000 ug/m3 (OEB 1)</td>
<td>Internal</td>
</tr>
</tbody>
</table>

Further information: RSEN
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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: 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.

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.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: powder

Color: white

Odor: sulfurous

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 explosive dust-air mixture during processing,
handled or other means.

Flammability (liquids) : Not applicable

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 : 1 g/cm³

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, dynamic : No data available

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 reac-
tions : 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

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

Acute toxicity
Not classified based on available information.

Components:

Cilastatin:
Acute oral toxicity : LD50 (Rat): > 10,000 mg/kg
LD50 (Mouse): > 10,000 mg/kg

Imipenem:
Acute oral toxicity : LD50 (Mouse): 10,000 mg/kg
Acute toxicity (other routes of administration) : LD50 (Rat): > 2,000 mg/kg
Application Route: Intravenous
LD50 (Mouse): 1,500 mg/kg
Application Route: Intravenous

Skin corrosion/irritation
Not classified based on available information.

Components:

Cilastatin:
Species : Rabbit
Result : No skin irritation

Serious eye damage/eye irritation
Causes serious eye irritation.

Components:

Cilastatin:
Species : Rabbit
Result : Moderate eye irritation

Respiratory or skin sensitization

Skin sensitization
Not classified based on available information.

Respiratory sensitization
May cause allergy or asthma symptoms or breathing difficulties if inhaled.
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Components:

Cilastatin:
Routes of exposure: Skin contact
Remarks: No data available
Routes of exposure: Inhalation
Remarks: No data available

Imipenem:
Remarks: May cause sensitization of susceptible persons by inhalation of aerosol or dust.
Routes of exposure: Skin contact
Remarks: Not classified due to lack of data.

Germ cell mutagenicity
Not classified based on available information.

Components:

Cilastatin:
Genotoxicity in vitro: Test Type: Microbial mutagenesis assay (Ames test)
Result: negative

Imipenem:
Genotoxicity in vitro: Test Type: In vitro mammalian cell gene mutation test
Test system: Chinese hamster lung cells
Result: negative
Test Type: reverse mutation assay
Result: negative
Test Type: unscheduled DNA synthesis assay
Result: negative
Test Type: Chromosomal aberration
Result: negative
Test Type: sister chromatid exchange assay
Result: negative
Genotoxicity in vivo: Test Type: In vivo micronucleus test
Species: Mouse
Application Route: Intravenous
Result: negative

Carcinogenicity
Not classified based on available information.

Reproductive toxicity
Suspected of damaging the unborn child.
Components:

Cilastatin:
Effects on fertility: Test Type: Fertility/early embryonic development
Application Route: Intravenous
Fertility: LOAEL: 1,000
Symptoms: No adverse effects.
Result: No effects on fertility and early embryonic development were detected.

Imipenem:
Effects on fertility:
Species: Rat, male and female
Application Route: Intravenous
Fertility: LOAEL: 80 mg/kg body weight
Symptoms: No adverse effects., Reduced fetal weight.
Result: No effects on fertility and early embryonic development were detected.

Test Type: Fertility/early embryonic development
Species: Rat, male and female
Application Route: Subcutaneous
Fertility: LOAEL: 320 mg/kg body weight
Symptoms: No adverse effects., Reduced fetal weight.
Result: No effects on fertility and early embryonic development were detected.

Effects on fetal development:
Test Type: Development
Species: Monkey
Application Route: Intravenous
Developmental Toxicity: LOAEL: 100 mg/kg body weight
Result: Embryotoxic effects and adverse effects on the offspring were detected., No teratogenic effects.

Test Type: Development
Species: Rabbit
Application Route: Intravenous
Developmental Toxicity: NOAEL: 60 mg/kg body weight
Result: No teratogenic effects.

Test Type: Development
Species: Rat
Application Route: Intravenous
Developmental Toxicity: NOAEL: 60 mg/kg body weight
Result: No teratogenic effects.

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

STOT-single exposure
Not classified based on available information.

STOT-repeated exposure
Not classified based on available information.
Repeated dose toxicity

Components:

Cilastatin:
Species : Rat
NOAEL : >= 500 mg/kg
Application Route : Intravenous
Exposure time : 90 Days
Remarks : No significant adverse effects were reported

Species : Monkey
NOAEL : >= 500 mg/kg
Application Route : Intravenous
Exposure time : 5 Weeks
Remarks : No significant adverse effects were reported

Imipenem:
Species : Monkey
NOAEL : 60 mg/kg
LOAEL : 150 mg/kg
Application Route : Intravenous
Exposure time : 6 Months
Target Organs : Kidney

Species : Monkey
NOAEL : 120 mg/kg
Application Route : Subcutaneous
Exposure time : 6 Months
Remarks : No significant adverse effects were reported

Species : Rat
NOAEL : 180 mg/kg
Application Route : Intravenous
Exposure time : 6 Months
Remarks : No significant adverse effects were reported

Species : Rabbit
LOAEL : 150 mg/kg
Application Route : Intravenous
Target Organs : Kidney

Aspiration toxicity
Not classified based on available information.

Experience with human exposure

Components:

Imipenem:
Inhalation : Symptoms: Nausea, Vomiting, Diarrhea, Fever, hypotension, Dizziness, Drowsiness, Convulsions, pruritis, Rash
Remarks: May cause sensitization of susceptible persons by inhalation of aerosol or dust.
ECOTOXICITY

COMPONENTS:

CILASTATIN:
Toxicity to fish: LC50 (Pimephales promelas (fathead minnow)): > 111 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): > 99 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

Toxicity to algae/aquatic plants: EC50 (Anabaena flos-aquae): > 99 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

EC50 (Pseudokirchneriella subcapitata (green algae)): > 99 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

NOEC (Anabaena flos-aquae): 99 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

NOEC (Pseudokirchneriella subcapitata (green algae)): 99 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

Toxicity to fish (Chronic toxicity): EC10 (Pimephales promelas (fathead minnow)): > 9.9 mg/l
Exposure time: 32 d
Method: OECD Test Guideline 210

Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity): EC10 (Daphnia magna (Water flea)): > 10 mg/l
Exposure time: 21 d
Method: OECD Test Guideline 211

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

IMIPENEM:
Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): > 78 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

Toxicity to algae/aquatic plants: EC50 (Anabaena flos-aquae (cyanobacterium)): 0.0046 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201
NOEC (Anabaena flos-aquae (cyanobacterium)): 0.002 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

EC50 (Pseudokirchneriella subcapitata (green algae)): > 74 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

NOEC (Pseudokirchneriella subcapitata (green algae)): 74 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

Toxicity to fish (Chronic toxicity):
NOEC (Pimephales promelas (fathead minnow)): 9.4 mg/l
Exposure time: 32 d
Method: OECD Test Guideline 210

Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity):
NOEC (Daphnia magna (Water flea)): 11 mg/l
Exposure time: 21 d
Method: OECD Test Guideline 211

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

Persistence and degradability

Components:

Cilastatin:
Biodegradability: Result: Not readily biodegradable.
Biodegradation: 27 %
Exposure time: 28 d
Method: OECD Test Guideline 301B

Imipenem:
Biodegradability: Result: Not readily biodegradable.
Biodegradation: 29 %
Exposure time: 28 d
Method: OECD Test Guideline 301B

Bioaccumulative potential

Components:

Cilastatin:
Partition coefficient: n-octanol/water: log Pow: -3.53

Imipenem:
Partition coefficient: n-octanol/water: log Pow: < -1
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octanol/water

Mobility in soil

Components:

Cilastatin:
Distribution among environmental compartments: log Koc: 2.3

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
UN number: UN 3077
Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Imipenem)
Class: 9
Packing group: III
Labels: 9

IATA-DGR
UN/ID No.: UN 3077
Proper shipping name: Environmentally hazardous substance, solid, n.o.s. (Imipenem)
Class: 9
Packing group: III
Labels: Miscellaneous
Packing instruction (cargo aircraft): 956
Packing instruction (passenger aircraft): 956
Environmentally hazardous: yes

IMDG-Code
UN number: UN 3077
Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Imipenem)
Class: 9
Packing group: III
Labels: 9
EmS Code: F-A, S-F
Marine pollutant: yes

**Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code**

Not applicable for product as supplied.

**Domestic regulation**

**TDG**

- UN number: UN 3077
- Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Imipenem)
- Class: 9
- Packing group: III
- Labels: 9
- ERG Code: 171
- Marine pollutant: yes (Imipenem)

**Special precautions for user**

The transport classification(s) provided herein are for informational purposes only, and solely based upon the properties of the unpackaged material as it is described within this Safety Data Sheet. Transportation classifications may vary by mode of transportation, package sizes, and variations in regional or country regulations.

**SECTION 15. REGULATORY INFORMATION**

The ingredients of this product are reported in the following inventories:

- AICS: not determined
- DSL: not determined
- IECSC: not determined

**SECTION 16. OTHER INFORMATION**

**Full text of other abbreviations**

AICS - 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 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 Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; 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;
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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; TECI - Thailand Existing Chemicals Inventory; 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


Revision Date: 08/27/2021
Date format: mm/dd/yyyy

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.

CA / Z8