MATERIAL SAFETY DATA SHEET

Product Name: Imipenem and Cilastatin for Injection

1. CHEMICAL PRODUCT AND COMPANY INFORMATION

Manufacturer Name And Address
Hospira Inc.
275 North Field Drive
Lake Forest, Illinois USA
60045

Hospira UK Limited
Queensway
Royal Leamington Spa
England

Emergency Telephone
CHEMTREC: North America: 800-424-9300;
International 1-703-527-3887; Australia (02) 8014 4880

Hospira, Inc., Non-Emergency
US: 224-212-2000; UK: 44 (0) 1926 834400

Product Name
Imipenem and Cilastatin for Injection

Synonyms

Cilastatin (2-Heptenoic acid, 7-[(2-amino-2-carboxyethyl)thio]-2-[[2,2-dimethylcyclopropyl]carbonyl]amino]-, [R-[R*,S*-](Z)]-

2. COMPOSITION/INFORMATION ON INGREDIENTS

Active Ingredient Name
Imipenem Monohydrate
Cilastatin Sodium

Chemical Formula
Imipenem: C_{12}H_{17}N_{3}O_{4}S \cdot H_{2}O Cilastatin: C_{16}H_{26}N_{2}O_{5}SNa

Preparation
Sodium hydrogen carbonate is added to buffer the formulation following reconstitution.

<table>
<thead>
<tr>
<th>Component</th>
<th>Approximate Percent by Weight</th>
<th>CAS Number</th>
<th>RTECS Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Hydrogen Carbonate</td>
<td>&lt;2</td>
<td>144-55-8</td>
<td>VZ0950000</td>
</tr>
<tr>
<td>Imipenem Monohydrate</td>
<td>49</td>
<td>6221-86-9</td>
<td>CL5446520</td>
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<td>Cilastatin Sodium</td>
<td>49</td>
<td>82009-34-5</td>
<td>VZ0950000</td>
</tr>
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</table>

3. HAZARD INFORMATION

Carcinogen List

<table>
<thead>
<tr>
<th>Substance</th>
<th>IARC</th>
<th>NTP</th>
<th>OSHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilastatin Sodium</td>
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<td>Not Listed</td>
<td>Not Listed</td>
</tr>
<tr>
<td>Imipenem Monohydrate</td>
<td>Not Listed</td>
<td>Not Listed</td>
<td>Not Listed</td>
</tr>
<tr>
<td>Sodium Hydrogen Carbonate</td>
<td>Not Listed</td>
<td>Not Listed</td>
<td>Not Listed</td>
</tr>
</tbody>
</table>

Emergency Overview
Imipenem and Cilastatin for Injection is a powder that contains imipenem (a thienamycin...
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antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I). It is a broad-spectrum antibacterial agent given by intravenous administration. In the workplace, this material should be considered potentially irritating to the skin, eyes and respiratory tract, and a potential sensitizer which may induce allergic reactions in persons known to be sensitized to penicillins and cephalosporins. Based on clinical use, possible target organs include the gastrointestinal system, skin, hematopoietic system, and liver.

Occupational Exposure Potential

Information on the absorption of this product via inhalation or skin contact is not available. Avoid dust or liquid aerosol generation and skin contact.

Signs and Symptoms

None known from occupational exposure. In clinical use, the most common adverse effects of imipenem/cilastatin include rash, seizures, pruritus, urticaria, eosinophilia, thrombocytosis, and elevated liver enzymes. Some patients with a history of penicillin hypersensitivity have experienced severe hypersensitivity reactions when treated with another beta-lactam antibiotic.

Medical Conditions Aggravated by Exposure

Pre-existing hypersensitivity to penicillins or cephalosporin antibiotics; pre-existing gastrointestinal, skin, hematopoietic, or liver ailments.

4. FIRST AID MEASURES

Eye contact

Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Skin contact

Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Inhalation

Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Ingestion

Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

5. FIRE FIGHTING MEASURES

Flammability

None anticipated. However, many organic powders are combustible at high temperature.

Fire & Explosion Hazard

None anticipated. As with all powders, minimize the creation of dusty environments.

Extinguishing media

As with any fire, use extinguishing media appropriate for primary cause of fire.

Special Fire Fighting Procedures

No special provisions required beyond normal fire fighting equipment such as flame and chemical resistant clothing and self contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Spill Cleanup and Disposal

For spilled powder, isolate area around spill. Put on suitable protective clothing and equipment as specified by site spill procedures. Collect the spilled powder using techniques that minimize powder migration. Clean affected area with soap and water. Absorb any liquid with an inert absorbent material (e.g. absorbent pad). Dispose of materials according to the applicable federal, state,
Product Name: Imipenem and Cilastatin for Injection

or local regulations. If a spill occurs after reconstitution, absorb liquid with suitable material and clean affected area with soap and water. Dispose of materials according to the applicable federal, state, or local regulations.

7. HANDLING AND STORAGE

Handling
No special handling required under conditions of normal product use.

Storage
No special storage required for hazard control. For product protection, follow storage recommendations noted on the product case label, the primary container label, or the product insert.

Special Precautions
No special precautions are required for hazard controls. Employees with known allergies to penicillin and cephalosporin antibiotics should consult a health and/or safety professional prior to working with open containers of this material.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Guidelines

<table>
<thead>
<tr>
<th>Component</th>
<th>Type</th>
<th>Exposure limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/m³ ppm µg/m³</td>
<td></td>
</tr>
<tr>
<td>Imipenem Monohydrate</td>
<td>Not Applicable</td>
<td>N/A N/A N/A</td>
</tr>
<tr>
<td>Cilastatin Sodium</td>
<td>Not Applicable</td>
<td>N/A N/A N/A</td>
</tr>
<tr>
<td>Sodium Hydrogen Carbonate</td>
<td>Not Applicable</td>
<td>N/A N/A N/A</td>
</tr>
</tbody>
</table>

Respiratory protection
Respiratory protection is normally not needed during intended product use. However, if the generation of dusts or aerosols is likely, and engineering controls are not considered adequate to control potential airborne exposures, the use of an approved air-purifying respirator with a HEPA cartridge (N95 or equivalent) is recommended under conditions where airborne dust or aerosol concentrations are not expected to be excessive. For uncontrolled release events, or if exposure levels are not known, provide respirators that offer a high protection factor such as a powered air purifying respirator or supplied air. A respiratory protection program that meets OSHA’s 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions require respirator use. Personnel who wear respirators should be fit tested and approved for respirator use as required.

Skin protection
If skin contact with the product formulation is likely, the use of latex or nitrile gloves is recommended.

Eye protection
Eye protection is normally not required during intended product use. However, if eye contact is likely to occur, the use of chemical safety goggles (as a minimum) is recommended.

Engineering Controls
Engineering controls are normally not needed during the normal use of this product.

9. PHYSICAL/CHEMICAL PROPERTIES

Appearance/Physical State Solid
Color Off white to yellowish white powder in a vial.
Odor NA
Odor Threshold: NA
pH: 6.5 - 8.5 when reconstituted
Melting point/Freezing point: NA
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<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Boiling Point/Boiling Point Range</td>
<td>NA</td>
</tr>
<tr>
<td>Evaporation Rate</td>
<td>NA</td>
</tr>
<tr>
<td>Flammability (solid, gas)</td>
<td>NA</td>
</tr>
<tr>
<td>Upper/Lower Flammability or Explosive Limits</td>
<td>NA</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>NA</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>NA</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>NA</td>
</tr>
<tr>
<td>Solubility</td>
<td>Water</td>
</tr>
<tr>
<td>Partition coefficient: n-octanol/water</td>
<td>NA</td>
</tr>
<tr>
<td>Auto-ignition temperature</td>
<td>NA</td>
</tr>
<tr>
<td>Decomposition temperature</td>
<td>NA</td>
</tr>
</tbody>
</table>

### 10. STABILITY AND REACTIVITY

**Reactivity**
Not determined.

**Chemical Stability**
Stable under standard use and storage conditions.

**Hazardous Reactions**
Not determined

**Conditions to avoid**
Strong oxidizers and strong bases

**Incompatibilities**
Not determined

**Hazardous decomposition products**
Not determined. During thermal decomposition, it may be possible to generate irritating vapors and/or toxic fumes of carbon oxides (COx), nitrogen oxides (NOx), or sulfur oxides (SOx).

**Hazardous Polymerization**
Not anticipated to occur with this product.

### 11. TOXICOLOGICAL INFORMATION

**Acute Toxicity**
Not determined for the product formulation. Information for the ingredients is as follows:

<table>
<thead>
<tr>
<th>Ingredient(s)</th>
<th>Percent</th>
<th>Test Type</th>
<th>Route of Administration</th>
<th>Value</th>
<th>Units</th>
<th>Species</th>
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<tbody>
<tr>
<td>Imipenem</td>
<td>100</td>
<td>LD50</td>
<td>Oral</td>
<td>&gt;5000</td>
<td>mg/kg</td>
<td>Rat Mouse</td>
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<tr>
<td>Imipenem</td>
<td>100</td>
<td>LD50</td>
<td>Intravenous</td>
<td>1972</td>
<td>mg/kg</td>
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<tr>
<td>Imipenem:Cilastatin (1:1)</td>
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<td>LDLo</td>
<td>Intravenous</td>
<td>751:1359</td>
<td>mg/kg</td>
<td>Mouse</td>
</tr>
<tr>
<td>Imipenem:Cilastatin (1:1)</td>
<td>50:50</td>
<td>LDLo</td>
<td>Intravenous</td>
<td>771:1583</td>
<td>mg/kg</td>
<td>Rat</td>
</tr>
<tr>
<td>Sodium Hydrogen Carbonate</td>
<td>100</td>
<td>LD50</td>
<td>Oral</td>
<td>4220</td>
<td>mg/kg</td>
<td>Rat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3360</td>
<td>mg/kg</td>
<td>Mouse</td>
</tr>
</tbody>
</table>

**Aspiration Hazard**
None anticipated from normal handling of the intact product.
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Dermal Irritation/Corrosion
None anticipated from normal handling of the intact product. However, inadvertent contact with this product formulation may be irritating to mucous membranes and the respiratory system.

Ocular Irritation/Corrosion
None anticipated from normal handling of the intact product. However, inadvertent contact of this product formulation with eyes may produce irritation with redness and discomfort.

Dermal or Respiratory Sensitization
None anticipated from normal handling of the intact product. One of the active ingredients in this product is a potential sensitizer which may induce allergic reactions in persons known to be sensitized to penicillins and cephalosporins. If known to be allergic to penicillins or cephalosporins, consult a health or safety professional prior to handling open containers of this product.

Reproductive Effects
Reproductive tests in male and female rats were conducted with imipenem-cilastatin sodium at intravenous dosages up to 80 mg/kg/day and at a subcutaneous dosage of 320 mg/kg/day. Slight decreases in live fetal body weight were noted at the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups. Teratology studies with cilastatin sodium at dosages of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day administered subcutaneously to rats showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at intravenous dosages of 15, 30 or 60 mg/kg/day and rats given imipenem at intravenous dosages of 225, 450, or 900 mg/kg/day. Teratology studies with imipenem-cilastatin sodium at intravenous dosages of 20 and 80, and a subcutaneous dosage of 320 mg/kg/day in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity. Imipenem-cilastatin sodium, when administered subcutaneously to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher (1000–4000 mg/day) caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora. A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at dosages of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given dosages of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When dosages of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 0.6 times the maximum recommended daily human dose of the intravenous formulation) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups. No adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, approximately equal to the highest recommended human dose. FDA Pregnancy Category C.

Mutagenicity
Genetic toxicity studies were performed in a variety of bacterial and mammalian tests in vivo and in vitro. The tests used were: V79 mammalian cell mutagenesis assay (imipenem-cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem-cilastatin sodium) and in vivo mouse...
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cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any evidence of genetic alterations.

Carcinogenicity  Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin.

Target Organ Effects  Based on clinical use, possible target organs include the possible target organs include the gastrointestinal system, skin, hematopoietic system, and liver.

12. ECOLOGICAL INFORMATION

Aquatic Toxicity  Not determined for product.

Persistence/Biodegradability  Not determined for product.

Bioaccumulation  Not determined for product.

Mobility in Soil  Not determined for product.

13. DISPOSAL CONSIDERATIONS

Waste Disposal  All waste materials must be properly characterized. Disposal should be performed in accordance with federal, state or local regulatory requirements.

Container Handling and Disposal  Dispose of container and unused contents in accordance with federal, state and local regulations.

14. TRANSPORTATION INFORMATION

ADR/ADG/ DOT STATUS:  Not regulated

IMDG STATUS:  Not regulated

ICAO/IATA STATUS:  Not regulated

Transport Comments:  None

15. REGULATORY INFORMATION

USA Regulations

<table>
<thead>
<tr>
<th>Substance</th>
<th>TSCA Status</th>
<th>CERCLA Status</th>
<th>SARA 302 Status</th>
<th>SARA 313 Status</th>
<th>PROP 65 Status</th>
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<tbody>
<tr>
<td>Cilastatin Sodium</td>
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<td>Imipenem Monohydrate</td>
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<tr>
<td>Sodium Hydrogen Carbonate</td>
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<td>Not Listed</td>
<td>Not Listed</td>
<td>Not Listed</td>
<td>Not Listed</td>
</tr>
</tbody>
</table>

RCRA Status  Not Listed

U.S. OSHA Classification  Possible Sensitizer

Classification  Target Organ Toxin

Possible Irritant
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GHS Classification

*In the EU, classification under GHS/CLP does not apply to certain substances and mixtures, such as medicinal products as defined in Directive 2001/83/EC, which are in the finished state, intended for the final user:

Hazard Class Not Applicable

Hazard Category Not Applicable

Signal Word Not Applicable

Symbol Not Applicable

Prevention P260 - Do not breathe dust/fume/gas/mist/vapors/spray.

Hazard Statement Not Applicable

Response: IF INHALED: If breathing is difficult, remove to fresh air and keep at rest in a position comfortable for breathing. If experiencing respiratory symptoms call a POISON CENTER or doctor/physician.

IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs, seek medical advice/attention. Wash contaminated clothing before reuse.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical attention. If skin irritation occurs, get medical advice/attention.

Get medical attention if you feel unwell.

EU Classification*

*Medicinal products are exempt from the requirements of the EU Dangerous Preparations Directive. Information provided below is for the pure drug substance Imipenem Monohydrate Cilastatin Sodium.

Classification(s): Not Applicable

Symbol: Not Applicable

Indication of Danger: Not Applicable

Risk Phrases: R00 - Not Applicable


16. OTHER INFORMATION:

Notes:
ACGIH TLV American Conference of Governmental Industrial Hygienists – Threshold Limit Value
CAS Chemical Abstracts Service Number
CERCLA US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act
DOT US Department of Transportation Regulations
EEL Employee Exposure Limit
IATA International Air Transport Association
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LD50 Dosage producing 50% mortality
NA Not applicable/Not available
NE Not established
NIOSH National Institute for Occupational Safety and Health
OSHA PEL US Occupational Safety and Health Administration – Permissible Exposure Limit
Prop 65 California Proposition 65
RCRA US EPA, Resource Conservation and Recovery Act
RTECS Registry of Toxic Effects of Chemical Substances
SARA Superfund Amendments and Reauthorization Act
STEL 15-minute Short Term Exposure Limit
TSCA Toxic Substance Control Act
TWA 8-hour Time Weighted Average

MSDS Coordinator: Hospira GEHS
Date Prepared: 09/03/2010
Obsolete Date: 11/10/2009

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