

1 IDENTIFICATION OF THE SUBSTANCE OR MIXTURE AND OF THE SUPPLIER

Product Name: Imipenem and Cilastatin for Injection

Distributed By: WG Critical Care, LLC.
120 Route 17 North
Suite 115
Paramus, NJ 07652 USA

Customer Service Phone Number: 1-888-493-0861
Emergency Phone Number: 1-866-562-4708 (ProPharma)

Product Use: Pharmaceutical
Product Type: Antibacterial
Container Information: Vial

2 HAZARDS IDENTIFICATION

Hazard Class and Category Code(s)	Hazard statement Code(s)
Resp. Sens. 1	H334
Skin Sens 1	H317

Hazard pictogram(s)	
Signal word	Danger
Hazard statement(s)	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. H317: May cause an allergic skin reaction.

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Precautionary statement(s)	P280: Wear protective gloves/protective clothing/eye protection/face protection. P261: Avoid breathing dust/fume. P304 + P340: IF INHALED: remove victim to fresh air and keep at rest in a position comfortable for breathing. P342 + P311: If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/ attention.
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Other Hazards: The incomplete combustion of the material can generate toxic fumes such as oxides of carbon and oxides of nitrogen (for details refer to section 5.2.).

3 COMPOSITION / INFORMATION ON INGREDIENTS

Ingredient	CAS No.
Cilastatin Sodium	81129-83-1
Imipenem Monohydrate	74431-23-5
Sodium Hydrogen Carbonate	144-55-8

In accordance with paragraph (i) of §1910.1200, the specific chemical identity and/or exact percentage (concentration) of composition has been withheld as a trade secret.

4 FIRST AID MEASURES

Ingestion	Rinse mouth and seek medical advice immediately. Do not attempt to give any solid or liquid by mouth if the exposed subject is unconscious or semi- unconscious.
Inhalation	Remove to fresh air and monitoring breathing. If breathing becomes difficult, give oxygen and call a physician. If breathing stops, give artificial respiration.
Skin contact	Remove contaminated clothing and replace them with clean and dry ones. Wash the exposed skin area immediately with mild soap and water. Seek medical attention in case of irritation.
Eyes contact	Wash out with fresh running water for at least 15 minutes. Ensure complete irrigation of the eyes by keeping eyelids well open. Consult a doctor.

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MOST IMPORTANT SYMPTOMS AND EFFECTS, BOTH ACUTE AND DELAYED

Acute	<i>Cilastatin sodium</i> : exposure to the substance can cause an allergic reaction . <i>Imipenem monohydrate</i> : the substance may cause skin, eye, and respiratory tract irritation and gastrointestinal disturbances .
Delayed	<i>Imipenem monohydrate</i> : possible hypersensitization and superinfections .

Information below refers to the final product

PRIMAXIN® (imipenem and cilastatin sodium) is generally well tolerated. The following adverse reactions were reported on 1,723 patients treated in clinical trials. Many of these patients were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN®.

Local Adverse Reactions: phlebitis/thrombophlebitis, infused vein pain, vein induration, infused vein infection.

Systemic Adverse Reactions: *gastrointestinal* (nausea, diarrhea, vomiting, tongue papillar hypertrophy, pseudomembranous colitis, hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, heartburn, pharyngeal pain, increased salivation); *CNS* (fever, dizziness, seizures somnolence, confusion, myoclonus, vertigo, headache, encephalopathy, paresthesia); *special senses* (transient hearing loss in patients with impaired hearing, tinnitus); *respiratory* (dyspnea, hyperventilation, thoracic spine pain); *cardiovascular* (hypotension, palpitations, tachycardia); *Renal* (oliguria/anuria, polyuria); *skin* (rash, pruritus, urticaria, skin texture changes, candidiasis, erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, pruritus vulvae; *Body as a whole* (polyarthralgia, asthenia/weakness).

Adverse Laboratory Changes: adverse laboratory changes, without regard to drug relationship, that were reported during clinical trials were: *hepatic* (increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH); *hemic* (increased eosinophils, positive Coombs' test, decreased WBC and neutrophils, increased WBC, increased platelets, decreased platelets, decreased, hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils); *electrolytes* (decreased serum sodium, increased potassium, increased chloride); *renal* (increased BUN, creatinine); *Urinalysis* (presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen).

INDICATION OF IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED

Inform your manager function, and enabled staff to first aid. Call immediately the Emergency number as reported in section 1.4 and consult a doctor

5 FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA

Suitable	Water spray, carbon dioxide, dry powder, foam.
Unsuitable	Do not use a heavy water stream.

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SPECIAL HAZARD ARISING FROM THE SUBSTANCE OR MIXTURE

Imipenem monohydrate: after 7.5 minutes it shows the presence of ammonia, methane, carbon dioxide, carbon monoxide and carbonyl sulfide **(3)**.

Cilastatin sodium: after 39.5 minutes, at an interval of heating ranging from 30 to 900 °C, it is detected the presence of carbon dioxide (CO₂), ammonia, carbon monoxide (CO),

ADVICE FOR FIRE-FIGHTERS

Use water spray or fog to cool exposed containers. Do not enter fire area without proper protective equipment, including respiratory protection.

6 ACCIDENTAL RELEASE MEASURE

PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES

For non-emergency personnel	Avoid inhalation and contact with eyes and skin. Alert Emergency Responders and tell them location and nature of hazard.
For emergency responders	Avoid inhalation and contact with eyes and skin. Wear approved respiratory protection, chemically compatible gloves and protective clothing and safety glasses. <u>MINOR SPILLS</u> Clean up all spills immediately. Use dry clean up procedures and avoid generating dust. Sweep up or vacuum up. Place spilled material in clean, dry, suitable, labeled container. <u>MAJOR SPILLS</u> Control personal contact by using protective equipment and dust respirator. Prevent spillage from entering drains, sewers or watercourses. Avoid generating dust. Recover product wherever possible. Put residues in labeled bags or other containers for disposal. If contamination of drains or waterways occurs, advise emergency services.



Personal protections in case of accidental spillage	Eye protection: Must wear proper eye protection. Skin protection: Tyvek coverall, safety shoes, gloves, forearm. Respiratory system protection: Filter system FFP2. Attention: for the choice of the material, take into consideration the possible individual allergic reactions.
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ENVIRONMENTAL PRECAUTIONS

Avoid to spillage the product in water and sewage systems. Use rugs cover manholes, bags of absorbent material.

METHODS AND MATERIAL FOR CONTAINMENT AND CLEANING UP

Avoid raising dust during collection and eliminating any source of ignition.
Ventilate area and wash areas affected only after the collection of the material. Avoid using oxidizing agents to wash affected areas.

7 HANDLING AND STORAGE

PRECAUTIONS FOR SAFE HANDLING

Measures to prevent fire	Use grounding procedures equipment. Avoid static discharges accumulation.
Measures to prevent aerosol and dust generation	Handle taking care to close handle bags and/or containers.
Measures to protect the environment	Keep away from drains.
Advice on general occupational hygiene	Do not eat, drink and smoke in work areas. Wash hands after use. Remove contaminated clothing and protective equipment before entering eating areas.

CONDITIONS FOR SAFE STORAGE, INCLUDING ANY INCOMPATIBILITIES

Store between 20-25 °C.

SPECIFIC END USE(S): N.D.

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8 EXPOSURE CONTROLS / PERSONAL PROTECTION

CONTROL PARAMETERS

Occupational Exposure limit values (OEL)	N.D.
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EXPOSURE CONTROLS

Appropriate Engineering controls	Analytical surveys are conducted to assess the concentration of dust in the work environment.
Personal protection	Eye protection: Must wear proper eye protection. Skin protection: Tyvek coverall, safety shoes, waterproof gloves forearm in latex (length 320 mm and thickness 0,4 mm) or neoprene gloves (length 300 mm and thickness 0,75 mm). Respiratory system protection: Filter system FFP2. Attention: for the choice of the material, take into consideration the possible individual allergic reactions.
Environmental Exposure Controls	N.A.

9 PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL STATE:	Solid	APPEARANCE:	White powder
VISCOSITY:	Not Available	ODOR:	Odorless
VAPOR PRESSURE:	Not Available	ODOR THRESHOLD:	Not Available
VAPOR DENSITY:	Not Available	pH:	6.5-8.5
RELATIVE DENSITY:	2.160 g/cm ³	MELTING POINT:	Not Available
FREEZING POINT:	Not Available	EVAPORATION RATE:	Not Available
FLASH POINT:	Imipenem monohydrate: 296,9 °C		
UPPER/LOWER FLAMMABILITY (UEL, LEL, OR MEC) OR EXPLOSIVE LIMITS	<i>Imipenem monohydrate:</i> 40 g/m³ . <i>Cilastatin sodium:</i> 150 g/m³ .		

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SOLUBILITY:	Imipenem monohydrate Water solubility: 10 mg/ml. Other solubilities: slightly soluble in methanol, practically insoluble in ethanol, in dimethylformamide, and in dimethyl sulfoxide (DMSO). Cilastatin sodium Soluble in water at 100 mM, and in DMSO at 10 mM. Soluble in methanol. Sodium hydrogen carbonate 1 M at 20 °C		
INITIAL BOILING POINT AND BOILING RANGE:	Imipenem monohydrate: 567,3 °C at 760 mmHg . Cilastatin sodium: 655 °C at 760 mmHg . Sodium hydrogen carbonate: 851 °C .		
AUTO-IGNITION TEMPERATURE:	Imipenem monohydrate Ignition temperature in layer: from 17.21 °C, the sample does not ignite until the maximum temperature of 400 °C. Auto ignition temperature in cloud: at room pressure the sample is non-flammable up to 450 °C. Cilastatin sodium Auto flammability in cloud is non-flammable at room pressure up to 430 °C. Ignition temperature in layer: at the temperature of 17.21 °C and density of charge equal to 0.51 g/cm³, the sample does not ignite until the maximum temperature of 400 °C.		
DECOMPOSITION TEMPERATURE:	Imipenem monohydrate: 97 °C . Cilastatin sodium: beginning of decomposition at 194 °C . Sodium hydrogen carbonate > 50°C.		
EXPLOSIVE LIMITS:	Explosion parameters: maximum pressure (Pmax) = 9,4 bar; maximum increase of rate pressure (dP/dt) _{max} = 614 bar/s; maximum value of Kst= 167 bar. m/s (St1class) .		
PARTITION COEFFICIENT (N-OCTANOL / WATER)	Imipenem monohydrate LogP: -0.770. Calc. LogP (KowWin): -1.17. Cilastatin sodium Log Pow: -1,177. Sodium hydrogen carbonate LogP: -4,01(TOXNET)		
FLAMMABILITY:	Not Available		

10 STABILITY AND REACTIVITY

REACTIVITY

See section 7.2.

CHEMICAL STABILITY

Stable under normal storage conditions (see section 7.2).

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**POSSIBILITY OF HAZARDOUS REACTIONS:**

Refer to section 9.1 "Decomposition Temperature".

CONDITIONS TO AVOID

Incompatibility and conditions to be avoided	Protect from moisture. Store in a dry place. Avoid accumulation of electrostatic charge. Connect to the circuit ground. Keep away from open flames, heat, direct lighting and auto ignition sources.
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INCOMPATIBLE MATERIALS

Avoid exposure to strong oxidizing agents .

HAZARDOUS DECOMPOSITION PRODUCTS: See section 5.2

11 TOXICOLOGICAL INFORMATION

INFORMATION ON TOXICOLOGICAL EFFECTS

Acute toxicity data of Imipenem and Cilastatin	Organism Rat Mouse *Intravenous	Test LD50 LD50	Route IV* IV*	Normalized Dose ≈1000mg/kg ≈1000mg/kg
Acute toxicity of Sodium Hydrogen Carbonate	Organism Rat	Test LD50	Route Oral	Normalized Dose 4220mg/kg
Skin corrosion/irritation	Cilastatin sodium may cause irritation . Imipenem can be harmful if absorbed through the skin and if in contact with eye .			
Respiratory or skin sensitization	Exposure to imipenem and cilastatin may cause allergic reactions (3, 2).			

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Toxicity after repeated exposure Imipenem and Cilastatin Sodium (7)	Principal subacute and Chronic toxicity studies with Primaxin®			
	<i>Duration</i>	<i>Species, Number/Sex/Group</i>	<i>Dosage Levels (mg/Kg/day)</i>	<i>Principal Effects Observed</i>
	5-Week,IV.,S.C.	Rat, 15	20/20, 80/80 I.V. 320/320 S.C.	No drug-included adverse effects
	5-Week,IV.,S.C.	Monkey,3	20/20, 60/60,I.V. 180/180 S.C.	No changes related to treatment.
	14-Week,IV.,S.C.	Rat, 15	20/20, 80/80 320/320	No changes related to treatment.
	14-Week,S.C.	Infant Monkey,3	20/20, 60/60,180/180	No adverse drug-included changes.
	10-Week,S.C.	Newborn Monkey,5M,3F	180/180	No drug-included adverse effects.
	6-Month,IV.,S.C.	Rat, 30	20/20, 80/80 I.V. 320/320 S.C.	No adverse effects observed.
	6-Month,IV.,S.C.	Monkey, 4	20/20, 60/60 I.V. 180/180 S.C.	No adverse effects observed.
Carcinogenicity	N.D.			

Germ cell mutagenicity of Imipenem and Cilastatin (7)	Principal genetic studies with Primaxin®			
	<i>Type of Study</i>	<i>Species, Number/Sex/Group</i>	<i>Dosage Levels (mg/Kg/day)</i>	<i>Principal Effects Observed</i>
	Mutagenic	V-79 cells	With S-9 ^{**} : 1,3,4,5,7,9,11 mM Without S-9: 3,5,10,15 mM	No mutagenic activity detected
	Mutagenic	Unscheduled DNA synthesis, Rat hepatocytes	3,10,14,22 mM final concentration in medium	No increase in labelled nuclei
	Mutagenic	<i>In vivo</i> cytogenetic mouse bone marrow	59, 197, 590 mg/kg	No chromosomal aberration seen
	Mutagenic	<i>In vitro</i> cytogenetic (range finding)	With and without S-9: 0.2, 0.67, 2.0, 6.7, 20 mM and 2.0, 6.7, 20.0, 67 µM	Increased incidence of sister chromatide exchanges; study repeated, and <i>in vitro</i> and <i>in vivo</i> sister chromatid exchanges studies performed
	Mutagenic	<i>In vitro</i> chromosomal aberration assay	With S-9: 8.5, 6.4, 4.2, 2.1, 1.1 mM; Without S-9: 21.2 1.2 17.0, 12.7, 8.5, 4.2 mM	Negative
^{**} Rat liver microsomal activation system				

Reproduction toxicity of Imipenem and Cilastatin (7)	Principal reproductive toxicity studies with Primaxin®			
	<i>Type of Study</i>	<i>Species, Number/Sex/Group</i>	<i>Dosage Levels (mg/Kg/day)</i>	<i>Principal Effects Observed</i>
	Teratology, IV	Mouse, 25	20/20, 80/80, 320/320	No teratogenic effect
	Teratology (with post-natal exam) IV/SC	Rat, 35	20/20, 80/80, 320/320	No teratogenic effect, no adverse effect postata growth or behavior
	Teratologic IV/SC	Cynomolgus Monkey, 11 (IV) 14 (SC)	IV 40/40 SC 160/160	Emesis, body weight loss, deaths, abortions at both dose levels; histologic examination of tissues showed no cause of death. No evidence of teratogenicity
	Teratology by infusion 45 (total)	Cynomolgus Monkey	100/100 (Days 21-30, 31-40, 41-50)	Drug infused daily at 3 mg/ml for 10-day periods: no apparent relationship between drug-induced toxicity (emesis) and embryotoxicity.

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12 ECOLOGICAL INFORMATION

TOXICITY

Imipenem Monohydrate :

Daphnia magna LC50: 100 mg/l/48 hours.

Sodium cilastatin :

Daphnia Magna EC50: 29,700 mg/l/48hours.

Sodium hydrogen carbonate . Short-term effects:

Fish LC50: 7550 mg/l/96 hours.

PERSISTENCE AND DEGRADABILITY

Imipenem monohydrate degrades rapidly

BIOACCUMULATIVE POTENTIAL

Imipenem Monohydrate

LogP: -0.770.

Calc. LogP (KowWin): -1.17.

Cilastatin sodium

Log Pow: -1,177.

Sodium Hyderogen Carbonate

LogPow: - 4,01

MOBILITY IN SOIL:

Not Available

RESULTS OF PBT AND VPVB ASSESSMENT:

Not Available

OTHER ADVERSE EFFECTS:

Not Available



13 DISPOSAL CONSIDERATIONS

WASTE TREATMENT METHODS:

- DISPOSAL OF WASTES:** Dispose of waste in accordance with local, state and federal regulations
- CONTAMINATED PACKAGING:** The container or packaging must be cleaned and rendered incapable of holding any substance. It can then be disposed of in a manner consistent with that of the substance it contained. In this instance the packaging can be disposed through a commercial waste collection service. Alternatively, the container or packaging can be recycled if the hazardous residues have been thoroughly cleaned or rendered nonhazardous. Do not reuse container.
- US EP WASTE NUMBER:** Not Applicable
- CALIFORNIA HAZARDOUS WASTE CODES:** Not Applicable

14 TRANSPORT INFORMATION

REGULATORY ORGANIZATIONS:

- DOT: Not Regulated IATA: Not regulated as a dangerous good
- ICAO: Not Regulated IMDG: Not regulated as a dangerous good
- RID: Not Regulated ADR: Not Regulated
- ADG: Not Regulated
- Special Precautions: NONE*

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15 REGULATORY INFORMATION

Below is selected regulatory information chosen primarily for possible WG Critical Care use. This section is not a complete analysis or reference to all applicable regulatory information. Please consider all applicable laws and regulations for your city / state / country.

US State Regulations and Right to Know Regulations

SARA 311/312 Hazards:	This product is not hazardous chemical under 29CFR 1910.1200 and therefore not covered by Title III of SARA
SARA 302:	No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302
SARA 313:	This material does not contain any chemical components with known CAS numbers that exceed the threshold (de minimis) reporting levels established by SARA Title III, Section 313
California Prop 65:	Not listed
OSHA Substance Specific	No

16 OTHER INFORMATION

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PUROPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

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END OF SAFETY DATA SHEET

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