MILLENNIUM

Revision Date: 10 March 2005

MATERIAL SAFETY DATA SHEET
VELCADE® (bortezomib) for Injection

Section 1 – Company and Material Identification

COMPANY IDENTIFICATION

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

For further product information contact: 1-866-VELCADE
In case of Emergency, contact: Chemtrec 1-800-424-9300

MATERIAL IDENTIFICATION

Product Name: VELCADE® (bortezomib) for Injection
Active ingredient: Bortezomib
Chemical name of active ingredient: [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid
Synonyms of active ingredient: PS-341, MLN-341, MG-341, NSC-681239

The following MSDS applies to the formulated lyophilized product only. If handling VELCADE® (bortezomib) for Injection in manufacturing situations, consult the MSDS for the active ingredient and take appropriate precautions.

Section 2 – Product Composition

Substance	CAS No.	% (by wt)
Bortezomib	179324-69-7	10%
Excipients (mannitol)		90%

Section 3 – Health Hazards

WARNING STATEMENT

CAUTION: Contains bortezomib, a pharmaceutically active ingredient. Handling should only be performed by personnel trained and familiar with handling of potent active pharmaceutical ingredients. Contents of vial may pose a health hazard only if exposure occurs, e.g., after a spill or leak. Toxic if inhaled or absorbed through the skin. Skin and eye irritant. Repeated occupational overexposure may cause fatigue and fever, and effects on the hematological (decreases in hemoglobin/anemia, blood counts and platelets), gastrointestinal (nausea, diarrhea,

vomiting, abdominal pain), and nervous systems (headache, peripheral neuropathy). May affect fertility based on animal toxicity studies. Avoid skin contact, eye contact, and inhalation.

Routes of Absorption
Skin contact, eye contact, inhalation, and accidental ingestion.

Eye and Skin
Based on irritation studies of the drug substance, VELCADE® (bortezomib) for Injection is expected to be a skin and eye irritant.

Systemic
The effects reported are from use of the drug product clinically or the testing of the drug substance in laboratory animals.

Acute
In patients given the drug, bortezomib produces many of the acute effects typical of drugs that kill rapidly growing cells, including effects on the hematological system, fatigue, nausea, vomiting, diarrhea, and fever. Other organ systems reported to be effected include the respiratory tract (shortness of breath), and nervous system (headache, dizziness, and peripheral neuropathy). Some of the acute effects may be delayed in onset, such as the effects on the hematological system, which are characterized by decreased white blood cells, platelets and red blood cells, and may occur several days or weeks following the acute exposure. These effects may potentially occur from acute (severe spill) or repeated overexposure in occupational settings.

Chronic
Based on other antineoplastic agents and data on bortezomib, the spectrum of effects after chronic exposure would be expected to be similar to those after acute exposure. Initial repeated dose studies in laboratory animals have shown similar effects as acute studies.

Reproductive and Developmental Toxicity
Bortezomib has not been evaluated for reproductive toxicity (effects on fertility). Repeated dose studies in laboratory animals have caused degenerative changes in the ovary and testes.

In developmental toxicity studies at low doses in laboratory animals (< 0.05 mg/kg/day by injection) during gestation, bortezomib at maternally toxic doses, was embryolethal and embryotoxic but did not cause a significant increase in malformations in the rat and rabbit. Because of the embryolethal effects at low doses, it should be considered a reproductive toxicant but not a teratogenic agent.

Mutagenicity
Studies evaluating gene mutation were negative (Ames gene mutation assay). Positive in vitro chromosomal aberration study in Chinese Hamster Ovary cells most likely due to pharmacological mechanism of action. Not a clastogen in vivo (mouse micronucleus assay).

Carcinogenicity
No data available.

Medical Conditions Aggravated by Exposure
None known or reported.

Occupational Exposure Limit
None currently established by US OSHA, NIOSH, ACGIH, or Millennium.

Section 4 – First Aid Precautions

Eye Contact
Immediately flush eyes thoroughly with water for at least 15 minutes and notify medical personnel and supervisor.

Skin Contact
Immediately wash thoroughly with soap and water for 15 minutes and notify medical personnel and notify supervisor.

Inhalation
Immediately move to fresh air and notify medical personnel and supervisor.

Ingestion
Immediately notify medical personnel and supervisor. Drink 2-3 glasses of water and contact medical personnel.

Section 5 – Fire Protection

Flammability/Explosivity
As a solid, not considered flammable. No explosivity data available. High concentrations of airborne finely divided organic particulates can potentially explode if ignited.

Extinguishing Media
Use water fog or fire extinguishing media suitable for Class A fires (e.g., multipurpose dry chemical or foam).

Special Fire Fighting Procedures
Wear full structural fire fighting protective clothing and NIOSH/MSHA-approved positive pressure, self-contained breathing apparatus. Decontaminate after use.

Section 6 – Spill and Release Measures

If material is released or spilled, cordon off spill area. Take proper precautions to minimize exposure by using appropriate personal protective equipment.

For small spills of powders (such as in a laboratory), wet material with water to reduce potential for dust generation and soak up material with absorbent, e.g., paper towels. For small spills of liquid reconstituted product, soak up material with absorbent, e.g., paper towels. In both cases, wash spill area thoroughly with soap and water. Small quantities of 70% ethanol and 10% bleach may also be used to clean work or spill surfaces.

For large spills in manufacturing, use an industrial vacuum cleaner equipped with a high efficiency particulate (HEPA) filter. Wear personal protective equipment for emergency situations (minimum of Tyvek or equivalent protective clothing, gloves, and a powered air-purifying respirator with NIOSH /MSHA approval for dusts and mists).

Dispose of all collected material in accordance with applicable local, state and federal waste disposal regulations.

Section 7 – Handling and Storage

Avoid contact with skin, eyes or clothing. Store in a well-ventilated area at controlled room temperature away from sources of ignition and incompatibles. Wash thoroughly after handling.

Section 8 – Exposure Control/Personal Protection

Occupational Exposure Category/Band
Millennium considers the active pharmaceutical ingredient to be a highly potent / toxic active pharmaceutical ingredient because of its significant potency and cytotoxicity.

Engineering Controls
When practicable, handle material in enclosed processes or in processes with effective and well-engineered local exhaust ventilation. The emphasis of control should be on little if any open handling and containment and control at the source of dust or aerosol generation. For re-constitution, the lyophilized powder should be handled in a Biological Safety Cabinet, a barrier isolator, ventilated enclosure, or other equivalent containment device.

Eye Protection
Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face.

Respiratory Protection
When possible, handle material in enclosed processes or containers. For reconstitution, when feasible, handle in a Biological Safety Cabinet, barrier/isolator, or ventilated balance enclosure using good work practices to contain product within these devices. In the laboratory, if it is properly handled with effective containment, respiratory protection may not be needed.

If conducting activities outside of containment where there is a potential for aerosolization of the drug product, use of an air-purifying respirator with NIOSH/MSHA approval for dusts and mists should be considered.

For manufacturing of the drug product, consult the MSDS for the drug substance/active ingredient for respiratory protection recommendations.

Skin Protection
Rubber gloves are recommended to minimize potential for skin contact when handling in dry form or in aqueous solutions. Double gloves should be considered. When the material is dissolved in an organic solvent, wear gloves that provide protection against the solvent. Wear lab coat or other protective overgarment. Base the choice of protection on the job activity and potential for skin contact.

Other
Wash hands, face and other potentially exposed areas immediately after handling material (especially before eating, drinking, or smoking). Decontaminate all protective equipment after use.

Section 9 – Physical/Chemical Properties

The following are physical/chemical properties of the drug product; consult MSDS for the drug substance for physical/chemical properties of the drug substance/active ingredient.

Appearance/color:	White powder
Molecular Weight:	Not applicable/mixture
pH:	Not applicable/solid
Boiling Point:	Not applicable/solid
Melting Point:	Approximately 165 degrees C
Vapor Pressure:	Negligible
Solubility in Water:	Approximately 80 mg/mL
Evaporation Rate:	Negligible
Specific Gravity:	No data available.
Vapor Density:	Negligible
Percent Volatile:	Negligible

Section 10 – Stability/Reactivity

Stability:	Pharmacologically stable.
Incompatability:	Not known.
Hazardous Polymerization:	Not known to occur
Hazardous Decomposition Products:	No data available.

Section 11 – Toxicological Information

See also Section 3. The data in this section are for the drug substance.

Acute Toxicity:
No single dose oral toxicity studies in rats or mice. Most studies conducted either by intravenous or intraperitoneal administration. In one study in the monkey, an oral dose of 0.7 mg/kg was fatal in a female monkey, but not in a male monkey tested at this dose. Based on this limited data and intravenous data indicating significant potential to be toxic or lethal at doses < 2 mg/kg in rats and mice, bortezomib should be considered highly acutely toxic.

Irritation/Sensitization:
Moderate to severe skin irritant based on studies in rabbits. Considered to be a severe eye irritant based on the skin irritation study. No studies assessing allergic skin potential.

Repeated dose studies:
Administration by intravenous injection has produced effects consistent with other cytotoxic drugs including effects on the gastrointestinal tract, hematological system, liver, peripheral nervous system, kidney and liver.

Developmental toxicity:
At low doses in laboratory animals (< 0.05 mg/kg/day by injection) during gestation, bortezomib at maternally toxic doses was embryolethal and embryotoxic but did not cause a significant increase in malformations in the rat and rabbit. Because of the embryolethal effects at low doses, it should be considered a reproductive toxicant but not a teratogenic agent.

Reproductive toxicity:
Bortezomib has not been evaluated for reproductive toxicity (effects on fertility). Repeated dose studies in laboratory animals have caused degenerative changes in the ovary and testes.

Mutagenicity:
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Carcinogenicity:
No data available.

Section 12 – Environmental Information

Persistence and Degradability
No data available.

Aquatic Toxicity
No data available.

Section 13 – Waste Disposal Methods

All wastes containing the material should be properly labeled. Dispose of any waste residues according to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

Section 14 – Transportation Information

Transport according to all local, state and Federal regulations.

Hazard Class
6.1

Proper Shipping Name
Medicine, solid, toxic, n.o.s. (VELCADE® (bortezomib) for Injection)

Packing Group
II

UN Number
3249

Section 15 – Regulatory Information

US OSHA
This MSDS complies with the requirements under 29 CFR 1910.1200

European Union (EU) Risk and Safety Phrases

R23/24/25	Toxic by inhalation, in contact with skin and if swallowed.
R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
S53	Avoid exposure – Obtain special instruction before use.

California Proposition 65
Not listed.

Canadian WHMIS

Drugs are exempt, however, if not a drug, the most appropriate classification for bortezomib would be D1A based on its potential to be cytotoxic and a reproductive or developmental toxicant

Section 16 – Other Information

No additional information.

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The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product.