SAFETY DATA SHEET

1. Identification

Product identifier **Velcade for injection**

Other means of identification

Product code Bortezomib drug product, MLN341, PS-341, LDP-341

Recommended use Pharmaceutical product.

This safety data sheet is written to provide health, safety and environmental information for people handling this formulated product in the workplace. It is not intended to provide information relevant to medicinal use of the product. In this instance patients should consult prescribing information/package insert/product label or consult their pharmacist or physician. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate safety data sheet for each ingredient.

Recommended restrictions All other uses.

Manufacturer/Importer/Supplier/Distributor information

Main Office Takeda Pharmaceutical Company Limited
1-1, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8668, Japan

SDS Information

US Office 40 Landsdowne Street, Cambridge, MA, 02139, USA

CH Office Thurgauerstrasse 130, 8152 Glattpark-Opfikon (Zurich), Switzerland

E-mail Takeda-SDS@takeda.com

Emergency phone number Call CHEMTREC Day or Night
Within USA and Canada: 1-800-424-9300
Outside USA and Canada: +1 703-741-5970 (collect calls accepted)
From anywhere in the world: +1 703-527-3887

2. Hazard(s) identification

Physical hazards Not classified.

Health hazards

Acute toxicity, oral	Category 2
Skin corrosion/irritation	Category 1C
Serious eye damage/eye irritation	Category 1
Reproductive toxicity	Category 2
Specific target organ toxicity, repeated exposure	Category 2

OSHA defined hazards Combustible dust

Label elements

Signal word Danger

Hazard statement May form combustible dust concentrations in air. Fatal if swallowed. Causes severe skin burns and eye damage. Suspected of damaging fertility or the unborn child. Causes damage to organs through prolonged or repeated exposure.

Precautionary statement

Prevention	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Wash thoroughly after handling. Do not eat, drink or smoke when using this product. Do not breathe dust. Wear protective gloves/protective clothing/eye protection/face protection.
Response	IF exposed or concerned: Get medical advice/attention. If swallowed: Rinse mouth. Do NOT induce vomiting. If on skin (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower. 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 inhaled: Remove person to fresh air and keep comfortable for breathing. Immediately call a poison center/doctor.
Storage	Store locked up.
Disposal	Dispose of contents/container in accordance with local/regional/national/international regulations.

Hazard(s) not otherwise classified (HNOC) None known.

Supplemental information Finished Pharmaceutical products in their final packages are not subject to OSHA labeling requirements.

3. Composition/information on ingredients

Mixtures

Chemical name	CAS number	%
Bortezomib	179324-69-7	Proprietary
Mannitol	69-65-8	Proprietary

Composition comments The exact concentrations of the above listed chemicals are being withheld as a trade secret.

4. First-aid measures

Inhalation Move to fresh air. Call a physician if symptoms develop or persist.

Skin contact Take off immediately all contaminated clothing. Rinse skin with water/shower. Call a physician or poison control center immediately. Chemical burns must be treated by a physician. Wash contaminated clothing before reuse.

Eye contact Do not rub eyes. Immediately flush eyes with plenty of water for at least 15 minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Call a physician or poison control center immediately.

Ingestion Call a physician or poison control center immediately. Rinse mouth. Do not induce vomiting. If vomiting occurs, keep head low so that stomach content doesn't get into the lungs. Do not use mouth-to-mouth method if victim ingested the substance. Induce artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device.

Most important symptoms/effects, acute and delayed Burning pain and severe corrosive skin damage. Causes serious eye damage. Symptoms may include stinging, tearing, redness, swelling, and blurred vision. Permanent eye damage including blindness could result. Dust may irritate the respiratory system. Prolonged exposure may cause chronic effects.

Indication of immediate medical attention and special treatment needed Provide general supportive measures and treat symptomatically. Chemical burns: Flush with water immediately. While flushing, remove clothes which do not adhere to affected area. Call an ambulance. Continue flushing during transport to hospital. Keep victim warm. Keep victim under observation. Symptoms may be delayed.

General information IF exposed or concerned: Get medical advice/attention. If you feel unwell, seek medical advice (show the label where possible). Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves. Show this safety data sheet to the doctor in attendance.

5. Fire-fighting measures

Suitable extinguishing media Avoid high pressure media which could cause the formation of a potentially explosible dust-air mixture. Water fog. Foam. Dry chemical powder. Carbon dioxide (CO2). Apply extinguishing media carefully to avoid creating airborne dust.

Unsuitable extinguishing media Do not use water jet as an extinguisher, as this will spread the fire.

Specific hazards arising from the chemical Explosion hazard: 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. During fire, gases hazardous to health may be formed.

Special protective equipment and precautions for firefighters Self-contained breathing apparatus and full protective clothing must be worn in case of fire.

Fire fighting equipment/instructions	In case of fire and/or explosion do not breathe fumes. Move containers from fire area if you can do so without risk.
Specific methods	Use standard firefighting procedures and consider the hazards of other involved materials.
General fire hazards	May form combustible dust concentrations in air.

6. Accidental release measures

Personal precautions, protective equipment and emergency procedures	Keep unnecessary personnel away. Use only non-sparking tools. 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. Wear appropriate protective equipment and clothing during clean-up. Do not breathe dust. Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits. Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. Ensure adequate ventilation. Local authorities should be advised if significant spillages cannot be contained. For personal protection, see section 8 of the SDS.
Methods and materials for containment and cleaning up	Eliminate all ignition sources (no smoking, flares, sparks, or flames in immediate area). Take precautionary measures against static discharge. Use only non-sparking tools. Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air). Collect dust using a vacuum cleaner equipped with HEPA filter. Stop the flow of material, if this is without risk. Large Spills: Wet down with water and dike for later disposal. Shovel the material into waste container. Following product recovery, flush area with water. Small Spills: Sweep up or vacuum up spillage and collect in suitable container for disposal. Clean surface thoroughly to remove residual contamination. Never return spills to original containers for re-use. For waste disposal, see section 13 of the SDS.
Environmental precautions	Avoid discharge into drains, water courses or onto the ground.

7. Handling and storage

Precautions for safe handling	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Minimize dust generation and accumulation. Avoid significant deposits of material, especially on horizontal surfaces, which may become airborne and form combustible dust clouds and may contribute to secondary explosions. Routine housekeeping should be instituted to ensure that dusts do not accumulate on surfaces. Dry powders can build static electricity charges when subjected to the friction of transfer and mixing operations. Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Combustible dust clouds may be created where operations produce fine material (dust). Handling and processing operations should be conducted in accordance with 'best practices' (e.g. NFPA-654). Explosion-proof general and local exhaust ventilation. Do not breathe dust. Do not get in eyes, on skin, or on clothing. Do not taste or swallow. When using, do not eat, drink or smoke. Pregnant or breastfeeding women must not handle this product. Should be handled in closed systems, if possible. Wear appropriate personal protective equipment. Wash hands thoroughly after handling. Observe good industrial hygiene practices.
Conditions for safe storage, including any incompatibilities	Store locked up. Keep containers tightly closed in a dry, cool and well-ventilated place. Store away from incompatible materials (see Section 10 of the SDS). When quality control required, follow the storage condition specified separately.

8. Exposure controls/personal protection

Occupational exposure limits	No exposure limits noted for ingredient(s).
Biological limit values	No biological exposure limits noted for the ingredient(s).
Exposure guidelines	Bortezomib (CAS 179324-69-7): OEL - 0.5 µg/m3 (Takeda internal value).
Appropriate engineering controls	Explosion-proof general and local exhaust ventilation. Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level. It is recommended that all dust control equipment such as local exhaust ventilation and material transport systems involved in handling of this product contain explosion relief vents or an explosion suppression system or an oxygen-deficient environment. Ensure that dust-handling systems (such as exhaust ducts, dust collectors, vessels, and processing equipment) are designed in a manner to prevent the escape of dust into the work area (i.e., there is no leakage from the equipment). Use only appropriately classified electrical equipment and powered industrial trucks. Eye wash facilities and emergency shower must be available when handling this product.

Individual protection measures, such as personal protective equipment

Eye/face protection	Wear safety glasses with side shields (or goggles).
Skin protection	
Hand protection	Wear appropriate chemical resistant gloves. Impervious oil/water/chemical-resistant gloves (nitrile, etc.). Gloves meeting EN374, ASTM F1001 or international equivalent standard are recommended.
Skin protection	
Other	Wear appropriate chemical resistant clothing. Use of an impervious apron is recommended.
Respiratory protection	Chemical respirator with organic vapor cartridge, full facepiece, dust and mist filter. Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits.
Thermal hazards	Wear appropriate thermal protective clothing, when necessary.
General hygiene considerations	Observe any medical surveillance requirements. When using, do not eat, drink or smoke. Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove contaminants.

9. Physical and chemical properties

Appearance	
Physical state	Solid.
Form	Cake or powder (lyophilized).
Color	White to off-white.
Odor	Property has not been measured.
Odor threshold	Not available.
pH	>= 4.0 - <= 7.0
Melting point/freezing point	Property has not been measured.
Initial boiling point and boiling range	Not applicable, material is a solid.
Flash point	Not applicable, material is a solid.
Evaporation rate	Not applicable, material is a solid.
Flammability (solid, gas)	Capable of catching on fire.
Upper/lower flammability or explosive limits	
Explosive limit - lower (%)	Not applicable, material is a solid.
Explosive limit - upper (%)	Not applicable, material is a solid.
Vapor pressure	Not applicable, material is a solid.
Vapor density	Not applicable, material is a solid.
Relative density	Property has not been measured.
Solubility(ies)	
Solubility (water)	Soluble (>= 0.1% w/v)
Partition coefficient (n-octanol/water)	Not applicable for mixtures.
Auto-ignition temperature	Property has not been measured.
Decomposition temperature	Property has not been measured.
Viscosity	Not applicable, material is a solid.
Other information	
Density	Property has not been measured.
Explosive properties	Not explosive.
Kinematic viscosity	Not applicable, material is a solid.
Oxidizing properties	Not oxidizing.

10. Stability and reactivity

Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport. Bortezomib oxidizes when in solution.

Chemical stability	Material is stable under normal conditions.
Possibility of hazardous reactions	No dangerous reaction known under conditions of normal use.
Conditions to avoid	Exposure to light. Keep away from heat, sparks and open flame. Contact with incompatible materials. Minimize dust generation and accumulation.
Incompatible materials	Strong oxidizing agents.
Hazardous decomposition products	No hazardous decomposition products are known.

11. Toxicological information

Information on likely routes of exposure

Inhalation	Dust may irritate respiratory system.
Skin contact	Causes severe skin burns.
Eye contact	Causes serious eye damage.
Ingestion	Fatal if swallowed. Causes digestive tract burns.
Symptoms related to the physical, chemical and toxicological characteristics	Burning pain and severe corrosive skin damage. Causes serious eye damage. Symptoms may include stinging, tearing, redness, swelling, and blurred vision. Permanent eye damage including blindness could result. Dust may irritate the respiratory system. Prolonged exposure may cause chronic effects.

Information on toxicological effects

Acute toxicity Fatal if swallowed.

Components	Species	Test Results
Bortezomib (CAS 179324-69-7)		
Acute		
Oral		
LD50	Rat	< 5 mg/kg (expert judgment)

Skin corrosion/irritation Causes severe skin burns.

Corrosivity

Bortezomib (CAS 179324-69-7) — Result: Acute dermal irritation study (OECD 404 (equivalent), rabbit, 4 h exposure): severe irritant and corrosive.

Serious eye damage/eye irritation Causes serious eye damage.

Respiratory or skin sensitization

Respiratory sensitization No data available.

Skin sensitization No data available.

Germ cell mutagenicity Not classified.

Germ cell mutagenicity: Ames test

Bortezomib (CAS 179324-69-7) — Result: Bortezomib showed no genotoxic activity in the Ames assay (OECD 471).

Germ cell mutagenicity: Chromosome Aberration

Bortezomib (CAS 179324-69-7) — In vitro. In CHO (Chinese hamster ovary) cells (OECD 473). Result: Clastogenic activity (chromosomal aberrations) was observed.The clastogenic activity is expected based on the compound's mechanism of action and its effect on the cell-cycle.

Germ cell mutagenicity: Micronucleus

Bortezomib (CAS 179324-69-7) — Result: Negative results were obtained in the in vivo micronucleus assay in mice (OECD 474).

Carcinogenicity No data available.

Bortezomib (CAS 179324-69-7) — Result: No studies available.

IARC Monographs. Overall Evaluation of Carcinogenicity

Not listed.

NTP Report on Carcinogens

Not listed.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1053)

Not listed.

Reproductive toxicity Suspected of damaging fertility or the unborn child.

Reproductivity

Bortezomib (CAS 179324-69-7)	Result: Embryo-fetal-developmental effects were both observed in rats and rabbits (at doses of 0.075 mg/kg and 0.05 mg/kg, respectively), but not below maternally toxic doses. Result: In a developmental toxicity study (OECD 414) in rats, the NOAEL for maternal and fetal effects was 0.050 mg/kg/day (0.3 mg/m2/day). Result: In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity and embryo-fetal development was 0.025 mg/kg/day (0.28 mg/m2/day).

Specific target organ toxicity - single exposure Not classified.
Bortezomib: Single dose IV studies (OECD 417) were conducted in mice, rats, dogs and monkeys, with the monkey being identified the most rigorous assessment of acute toxicity. In the cynomolgus monkey, the maximum tolerated dose (MTD) was 1.2 mg/m2 (0.1 mg/kg) and the minimum lethal dose (MLD) was 3.0 mg/m2 (0.25 mg/kg). Mouse MTD IV is 1.0 mg/kg; rat MTD IV is 0.10 mg/kg and dog MTD IV is 0.18 mg/kg.

Specific target organ toxicity - repeated exposure May cause damage to organs through prolonged or repeated exposure.
Bortezomib: The MTD in a 6-month repeat dose study in rats was 0.10 mg/kg (0.6 mg/m2). Target organs were the GI tract (at ≥0.10 mg/kg) and the hematopoietic and lymphoid systems (at ≥0.05 mg/kg). In a 9-month (13 cycles) IV repeat dose studies in cynomolgus monkeys, a NOAEL was not identified but the MTD was defined as 0.05 mg/kg, based on target organ toxicity observed in the bone marrow, lymphoid tissue (at ≥ 0.05 mg/kg) and the peripheral nervous system, kidney, and GI tract (at 0.075 mg/kg). Incomplete reversibility of the toxic effects was observed in both species.

Aspiration hazard Not relevant, due to the form of the product.

Chronic effects May cause damage to organs through prolonged or repeated exposure.

Further information No data available.

12. Ecological information

Ecotoxicity Not expected to be harmful to aquatic organisms.

Persistence and degradability No data is available on the degradability of any ingredients in the mixture.

Bioaccumulative potential

Partition coefficient n-octanol / water (log Kow)

Bortezomib (CAS 179324-69-7)	2.004

Mobility in soil No data available.

Other adverse effects No data available.

13. Disposal considerations

Disposal instructions Collect and reclaim or dispose in sealed containers at licensed waste disposal site. Dispose of contents/container in accordance with local/regional/national/international regulations.

Local disposal regulations Dispose in accordance with all applicable regulations.

Hazardous waste code The waste code should be assigned in discussion between the user, the producer and the waste disposal company.

Waste from residues / unused products Dispose of in accordance with local regulations. Empty containers or liners may retain some product residues. This material and its container must be disposed of in a safe manner (see: Disposal instructions).

Contaminated packaging Since emptied containers may retain product residue, follow label warnings even after container is emptied. Empty containers should be taken to an approved waste handling site for recycling or disposal.

14. Transport information

DOT

UN number	UN2928
UN proper shipping name	Toxic solids, corrosive, organic, n.o.s. (Bortezomib)
Transport hazard class(es)	
Class	6.1
Subsidiary risk	8
Label(s)	6.1, 8
Packing group	II

Environmental hazards

Marine pollutant No.

Special precautions for user Read safety instructions, SDS and emergency procedures before handling.

Special provisions IB6, IP2, T3, TP33

Packaging exceptions 153

Packaging non bulk 212

Packaging bulk 242

IATA

UN number UN2928

UN proper shipping name Toxic solid, corrosive, organic, n.o.s. (Bortezomib)

Transport hazard class(es)

Class 6.1

Subsidiary risk 8

Packing group II

Environmental hazards No.

ERG Code 6C

Special precautions for user Read safety instructions, SDS and emergency procedures before handling.

IMDG

UN number UN2928

UN proper shipping name TOXIC SOLID, CORROSIVE, ORGANIC, N.O.S. (Bortezomib)

Transport hazard class(es)

Class 6.1

Subsidiary risk 8

Packing group II

Environmental hazards

Marine pollutant No.

EmS F-A, S-B

Special precautions for user Read safety instructions, SDS and emergency procedures before handling.

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code Not applicable.

15. Regulatory information

US federal regulations This product is a "Hazardous Chemical" as defined by the OSHA Hazard Communication Standard, 29 CFR 1910.1200. This product may only be used for TSCA Exempt purposes such as R&D or Food, Drug or Cosmetic use.
All components are listed on or exempt from the U.S. EPA TSCA Inventory List.

TSCA Section 12(b) Export Notification (40 CFR 707, Subpt. D)

Not regulated.

CERCLA Hazardous Substance List (40 CFR 302.4)

Not listed.

SARA 304 Emergency release notification

Not regulated.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1053)

Not listed.

Toxic Substances Control Act (TSCA) All components are either listed on the TSCA 8(b) inventory and designated “active” or exempt from listing.

Superfund Amendments and Reauthorization Act of 1986 (SARA)

SARA 302 Extremely hazardous substance

Not listed.

SARA 311/312 Hazardous chemical No (Exempt)

SARA 313 (TRI reporting)

Not regulated.

Other federal regulations

Clean Air Act (CAA) Section 112 Hazardous Air Pollutants (HAPs) List

Not regulated.

Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130)

Not regulated.

Safe Drinking Water Act (SDWA) Not regulated.

US state regulations

US. Massachusetts RTK - Substance List

Not regulated.

US. New Jersey Worker and Community Right-to-Know Act

Not listed.

US. Pennsylvania Worker and Community Right-to-Know Law

Not listed.

US. Rhode Island RTK

Not regulated.

California Proposition 65

California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): This material is not known to contain any chemicals currently listed as carcinogens or reproductive toxins. For more information go to www.P65Warnings.ca.gov.

16. Other information, including date of preparation or last revision

Issue date	13-April-2022
Revision date	15-March-2023
Version #	02
Further information	Refer to: OSHA 3371-08 2009, Hazard Communication Guidance for Combustible Dusts NFPA 654, Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustible Particulate Solids
List of abbreviations	GI tract: Gastrointestinal tract. IV: Intravenous. LD50: Lethal Dose 50%. MTD: Maximum tolerated dose. OEL: Occupational Exposure Limit.
References	HSDB® - Hazardous Substances Data Bank In-house data
Disclaimer	Takeda Pharmaceutical Company Limited cannot anticipate all conditions under which this information and its product, or the products of other manufacturers in combination with its product, may be used. It is the user's responsibility to ensure safe conditions for handling, storage and disposal of the product, and to assume liability for loss, injury, damage or expense due to improper use. The information in the sheet was written based on the best knowledge and experience currently available.
This SDS contains revisions in the following section(s):	All sections.