PACKAGE LEAFLET

BORTMEX
BORTEZOMIB 3,5 MG

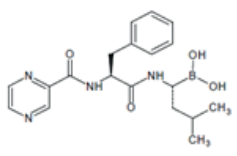
Powder, lyophilized, solution for injection for subcutaneous use

MADE IN ARGENTINA **PRESCRIPTION ONLY MEDICINE**

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Bortezomib.....3,5 mg
Mannitol.....35,0 mg

THERAPEUTIC ACTION
Antineoplastic agents, other antineoplastic agents
ATC Classification: L01XX32
Chemical structure and Molecular formula:



$C_{19}H_{25}BN_4O_4$

INDICATIONS
- Treatment of patients with multiple myeloma
- Treatment of patients with mantle cell lymphoma who have received prior therapy and/or have recurrence or refractoriness.

PHARMACOLOGY/PROPERTIES

Mechanism of Action
Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signaling cascades within the cell, ultimately resulting in cancer cell death. Bortezomib is highly selective for the proteasome. At 10 µM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a t½ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.
Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumorigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.
Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumor growth in vivo in many preclinical tumor models, including multiple myeloma.
Data from in vitro, ex-vivo, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

DRUG ACTION
Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The proteasome-ubiquitin pathway plays an essential role in regulating the intracellular concentration of specific proteins, thus maintaining homeostasis between cells. Inhibition of the 26S proteasome prevents this intended proteolysis which can affect multiple signaling cascades in the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have shown that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor development in vitro in preclinical tumor models, including multiple myeloma.

PHARMACOKINETICS
Absorption
Following intravenous bolus administration of a 1.0 mg/m² and 1.3 mg/m² dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50 mL/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose.
Following an intravenous bolus or subcutaneous injection of a dose of 1.3 mg/m² in patients with multiple myeloma (n = 14 in the intravenous treatment group, n = 17 in the subcutaneous treatment group), the total systemic exposure after repeated dose administration (AUClast) was equivalent for intravenous and subcutaneous administrations. Cmax after subcutaneous administration (20.4 ng/ml) was lower than intravenous administration (223 ng/ml). The geometric mean ratio of AUClast was 0.99 and the 90% confidence intervals were between 80.18% - 122.80%.

Distribution
The mean volume of distribution (Vd) of bortezomib ranged from 1,659 to 3,294 liters after intravenous administration of a single or repeated dose of 1.0 milligram/m² or 1.3 milligram/m² to patients with multiple myeloma. This suggests that bortezomib distributes extensively to peripheral tissues. Over the bortezomib concentration range of 0.01 to 1.0 microgram/milliliter, in vitro protein binding averaged 82.9%. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.
Biotransformation
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.
Elimination
The mean elimination half-life (t½) of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly after the first dose compared to subsequent doses. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m2 and 1.3 mg/m², respectively, and ranged from 15 to 32 L/hour and from 18 to 32 L/hour following subsequent doses for doses of 1 and 1.3 mg/m², respectively.
Special Populations
Hepatic impairment
When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored.
Renal impairment
A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mL/min/1.73 m², n=12), Mild (CrCL=40-59 mL/min/1.73 m², n=10), Moderate (CrCL=20-39 mL/min/1.73 m², n=9), and Severe (CrCL < 20 mL/min/1.73 m², n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m² of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups.

DOSAGE AND ADMINISTRATION
Treatment should be initiated and administered under the supervision of a qualified physician experienced in the use of chemotherapy drugs. Bortezomib must be reconstituted by a healthcare professional.
Dosage in the treatment of progressive multiple myeloma (patients who have received at least one previous treatment).
Monotherapy
Bortezomib 3.5 mg powder for solution for injection is administered intravenously or subcutaneously at the recommended dose of 1.3 milligrams/m² body surface area twice weekly for two weeks on days 1, 4, 8 and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of Bortezomib following confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of Bortezomib therapy. At least 72 hours should elapse between consecutive doses of Bortezomib.
Dose adjustments during treatment and re-initiation of treatment for monotherapy
Bortezomib treatment must be withheld at the onset of any Grade 3 non-hematological or any Grade 4 hematological toxicities, excluding neuropathy as discussed below (see also section 4.4). Once the symptoms of the toxicity have resolved, bortezomib treatment may be re-initiated at a 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
Neuropathic pain and/or peripheral neuropathy
Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1 (see section 4.4). Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

Table 1: Recommended dose modifications* for bortezomib-related neuropathy

Severity of Neuropathy	Modification of Dose
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function)	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))	Reduce Bortezomib for Injection to 1 mg/m² or Modify Bortezomib treatment schedule to 1.3 mg/m² once per week.
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL)	Withhold Bortezomib for Injection therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Bortezomib for Injection at 0.7 mg/m2 once per week.
Grade 4 (life-threatening consequences, urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue Bortezomib

Combination therapy with pegylated liposomal doxorubicin
Bortezomib is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib.
Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the Bortezomib treatment cycle as a 1-hour intravenous infusion administered after the Bortezomib injection.
Up to 8 cycles of this combination therapy can be administered as long as patients have not progressed and tolerate treatment. Patients achieving a complete response can continue treatment for at least 2 cycles after the first evidence of complete response, even if this requires treatment for more than 8 cycles. Patients whose paraprotein levels continue to decline after 8 cycles may also continue as long as treatment is tolerated, and patients continue to respond to treatment.
Combination therapy with dexamethasone liposomal doxorubicin
Bortezomib 3.5 mg powder for solution for injection is administered intravenously or subcutaneously at the recommended dose of 1.3 milligrams/m² body surface area twice weekly for two weeks on days 1, 4, 8 and 11. of a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib.
Dexamethasone is administered orally at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the Bortezomib treatment cycle.
Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.
Dose adjustments for combination therapy for patients with progressive multiple myeloma
For information on Bortezomib dose adjustments in combination therapy, follow dose modification guidelines described under monotherapy above.
Dose in previously untreated multiple myeloma patients not eligible for hematopoietic stem cell transplantation
Combination therapy with melphalan and prednisone
Bortezomib 3.5 mg powder for solution for injection is administered intravenously or subcutaneously in combination with melphalan and oral prednisone as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, Bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, Bortezomib is administered once weekly on days 1, 8, 22 and 29. At least 72 hours should elapse between consecutive doses of Bortezomib.
Melphalan and prednisone should both be administered orally on days 1, 2, 3, and 4 of the first week of each Bortezomib treatment cycle.
Nine treatment cycles of this combination treatment are administered.

Table 2: Recommended Bortezomib dose in combination with melphalan and prednisone

Week	1				2		3	4		5		6
Bortezomib (1.3 mg/m²)	Day 1	–	–	Day 4	Day 8	Day 11	Rest period	Day 22	Day 25	Day 29	Day 32	Rest period
Melphalan (9 mg/m²) Prednisone (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	–	–	Rest period	–	–	–	–	Rest period

Once weekly BORTEZOMIB (cycles 5-9)

Week	1				2	3	4	5	6
Bortezomib (1.3 mg/m²)	Day 1	–	–	–	Day 8	Rest period	Day 22	Day 29	Rest period
Melphalan (9 mg/m²) Prednisone (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	–	Rest period	–	–	Rest period

Dose adjustments during therapy and re-initiation of treatment for combination therapy with melphalan and prednisone
Prior to initiating a new cycle of therapy in combination with melphalan and prednisone:
- Platelet counts should be ≥70 x 10^9 /L and the ANC should be ≥ 1.0 x 10^9 /L.
- Non-hematological toxicities should have resolved to Grade 1 or baseline.

Table 3: Dose modifications during subsequent therapy cycles of Bortezomib in combination with melphalan and prednisone

Toxicity	Dose Modification or Delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle.	Consider reduction of the melphalan dose by 25% in the next cycle.
If platelet counts ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a Bortezomib dosing day (other than day 1)	Bortezomib therapy should be withheld
If several Bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²)
Grade ≥ 3 non-hematological toxicities	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in Table 1.

Dose in previously untreated multiple myeloma patients eligible for hematopoietic stem cell transplantation (induction therapy).
Combination therapy with dexamethasone
Bortezomib 3.5 mg powder for solution for injection is administered intravenously or subcutaneously at the recommended dose of 1.3 milligrams/m² body surface area twice weekly for two weeks on days 1, 4, 8 and 11 of a 21-day treatment cycle. This 3-week period is considered one therapy cycle. At least 72 hours should elapse between consecutive doses of Bortezomib.
Dexamethasone is administered orally at a dose of 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the Bortezomib therapy cycle.
Four-week treatment cycles of this combination therapy are administered.
Combination therapy with dexamethasone and thalidomide
Bortezomib 3.5 mg powder for solution for injection is administered intravenously or subcutaneously at the recommended dose of 1.3 milligrams/m² body surface area twice weekly for two weeks on days 1, 4, 8 and 11 of a 28-day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib.
Dexamethasone is administered orally at a dose of 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the Bortezomib therapy cycle. Four-week treatment cycles of this combination therapy are administered.
Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 4). Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 4: Dose for Bortezomib combination therapy for patients with previously untreated multiple myeloma eligible for hematopoietic stem cell transplantation

Bz + Dx	**Cycles 1 to 4**				
	Week	**1**		**2**	**3**
	Bz (1.3 mg/m²)	Day 1, 4		Day 8, 11	Rest period
	Dx 40 mg	Day 1, 2, 3, 4		Day 8, 9, 10, 11	-
Bz+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**Week**
	Bz (1.3 mg/m²)	Day 1, 4	Day 8, 11	Rest period	Rest period
	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycle 2 to 4[b]				
	Bz (1.3 mg/m²)	Day 1, 4	Day 8, 11	Rest period	Rest period
	T 200 mg	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

Bz= Bortezomib; Dx=dexamethasone; T=thalidomide
[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.
[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles.

Dose adjustments for transplant eligible patients
When Bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities.
Dose for patients with previously untreated mantle cell lymphoma (MCL)
Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (BzR-CAP)
Bortezomib is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Six bortezomib cycles are recommended, although for patients with a response first documented at cycle 6, two additional bortezomib cycles may be given. At least 72 hours should elapse between consecutive doses of Bortezomib.
The following medicinal products are administered on day 1 of each bortezomib 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m², cyclophosphamide at 750 mg/m² and doxorubicin at 50 mg/m².
Prednisone is administered orally at 100 mg/m² on days 1, 2, 3, 4 and 5 of each bortezomib treatment cycle.
Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma
Prior to initiating a new cycle of therapy:
- Platelet counts should be ≥ 100,000 cells/µL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/µL
- Platelet counts should be ≥ 75,000 cells/µL in patients with bone marrow infiltration or splenic sequestration
- Hemoglobin ≥ 8 g/dL
- Non-hematological toxicities should have resolved to Grade 1 or baseline.

Bortezomib treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-hematological toxicities (excluding neuropathy) or ≥ Grade 3 hematological toxicities.
For dose adjustments, see Table 5 below.
Granulocyte colony stimulating factors may be administered for hematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 5: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	Posology modification or delay
Hematological toxicity	
≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/µL	• Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL. • If, after Bortezomib has been held, the toxicity does not resolve, as defined above, then Bortezomib must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, Bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²).
If platelet counts < 25,000 cells/µL. or ANC < 750 cells/µL on a Bortezomib dosing day (other than Day 1 of each cycle)	• Bortezomib therapy should be withheld
Grade ≥ 3 non-hematological toxicities considered to be related to Bortezomib	• Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, Bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in Table 1.

Special populations
Elderly
There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age with multiple myeloma or with mental cell lymphoma.
There are no studies on the use of bortezomib in elderly patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with hematopoietic stem cell transplantation.
Therefore. no dose recommendations can be made in this population. In a study in previously untreated mantle cell lymphoma patients, 42.9% and 10.4% of patients exposed to bortezomib were in the range 65-74 years and ≥ 75 years of age, respectively. In patients aged ≥ 75 years, both regimens, BzR-CAP as well as R-CHOP, were less tolerated.
Hepatic impairment
Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on Bortezomib at a reduced dose of 0.7 mg/m2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² may be considered based on patient tolerability.

Table 6: Recommended starting dose modification for Bortezomib in patients with hepatic impairment

Grade of hepatic impairment*	Bilirubin level	SGOT (AST) levels	Modification of starting dose
Mild	≤ 1.0x LSN	> ULN	None
	> 1.0x-1.5x LSN	Any	None
Moderate	> 1.5x-3x LSN	Any	Reduce Bortezomib to 0.7 mg/m² in the first treatment cycle.
Severe	> 3x LSN	Any	Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.
* Based on NCI Organ Dysfunction Working Group classification for categorizing hepatic impairment (mild, moderate, severe).

Renal impairment
The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 mL/min/1.73 m²); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20 ml/min/1.73 m²). Since dialysis may reduce bortezomib concentrations, Bortezomib should be administered after the dialysis procedure.
Pediatric population
The safety and efficacy of bortezomib in children below 18 years of age have not been established. Currently no data is available.

METHOD OF ADMINISTRATION
Precautions for administration:
Bortezomib is antineoplastic. Care must be taken during handling and preparation. Appropriate aseptic techniques should be used. The use of gloves and protective clothing is recommended in order to avoid contact with the skin. Local skin irritation has been reported in 5% of patients. But Bortezomib extravasation was not associated with tissue damage.
Reconstitution/ Preparation for Intravenous Administration Prior to Use: reconstitute the contents of each vial with 3.5 ml of 0.9% sodium chloride solution for injection. The reconstituted product should be a clear, colorless solution.
Before administration, and whenever the container and the solution allow it, parenteral medicinal products must be visually controlled to ensure they do not contain particulate matter or discoloration. If any discoloration or particulate matter is observed, the reconstituted product should not be used.
Reconstitution/ Preparation for Subcutaneous Administration Prior to Use: reconstitute he contents of each vial with 1.4 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection to the vial containing the Bortezomib powder. The reconstituted product should be a clear, colorless solution.
Prior to administration, visually inspect the solution for particulate matter and discoloration. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

CONTRAINDICATIONS
Hypersensitivity to the active substance, to boron or to any of the excipients.
Acute diffuse infiltrative pulmonary and pericardial disease.

WARNINGS
When Bortezomib is given in combination with other medicinal products, the Summary of Product Characteristics of these other medicinal products must be consulted prior to initiation of treatment with BORTEZOMIB. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed.

Intrathecal administration
There have been fatal cases of inadvertent intrathecal administration of bortezomib.
Bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use.

BORTEZOMIB SHOULD NOT BE ADMINISTERED INTRATHECALLY.

Gastrointestinal toxicity
Gastrointestinal toxicity, including nausea, diarrhea, vomiting and constipation are very common with bortezomib treatment. Cases of ileus have been uncommonly reported. Therefore, patients who experience constipation should be closely monitored.
Hematological toxicity
Bortezomib treatment is very commonly associated with hematological toxicities (thrombocytopenia, neutropenia and anemia). In studies in patients with relapsed multiple myeloma treated with bortezomib and in patients with previously untreated MCL treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BzR-CAP), one of the most common hematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir

measured was approximately 40% of baseline in the single-agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/µl, 90% of 21 patients had a count ≤ 25,000/µl during the study, including 14% < 10,000/µl; in contrast, with a baseline platelet count > 75,000/µl, only 14% of 309 patients had a count ≤ 25,000/µl during the study.

Gastrointestinal and intracerebral hemorrhage have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib.

Bortezomib therapy should be withheld when the platelet count is < 25,000/µl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl.

Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with bortezomib.

Hepatitis B virus (HBV) reactivation and infection

When rituximab is used in combination with bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with bortezomib.

Antiviral prophylaxis should be considered.

Progressive multifocal leukoencephalopathy (PML)

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.

Treatment with bortezomib is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule or route of administration to subcutaneous. Neuropathy has been managed with supportive care and other therapies.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving bortezomib in combination with medicinal products known to be associated with neuropathy (e.g., thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited. Limited information is available on autonomic nervous system (ANS) neuropathy and its contribution to these adverse effects.

Heart failure

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

Electrocardiogram investigations

There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib.

Some of these events have been fatal. A pre-treatment chest x-ray is recommended to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), a prompt diagnostic evaluation should be performed, and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing bortezomib therapy.

The specific regimen with concomitant administration of Daunorubicin and Bortezomib with high-dose cytarabine (2 g/m² per day) by continuous infusion over 24 hours is not recommended.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment
should be monitored closely.

Hepatic impairment

Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.

Hepatic reactions

Rare cases of hepatic failure have been reported in patients receiving bortezomib and concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib.

Tumor lysis syndrome

Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of tumor lysis syndrome may occur. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken.

Concomitant medicinal products

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.

Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycemics.

Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% (CI90% [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously).

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

Patients with oral antidiabetic medication, treated with Bortezomib, may require strict glycemic monitoring with adjustment of the antidiabetic dose.

Fertility, pregnancy and lactation

Contraception in males and females

Male patients and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.

Pregnancy

No clinical data are available for bortezomib with regards to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

In non-clinical studies, bortezomib had no effects on embryonal/fetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of bortezomib on parturition and post-natal development were not conducted (see section 5.3). Bortezomib should not be used during pregnancy unless the clinical condition of the woman requires treatment with bortezomib.

If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of potential for hazard to the fetus.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the thalidomide pregnancy prevention program are met. Patients receiving bortezomib in combination with thalidomide should adhere to the pregnancy prevention program of thalidomide. Refer to the Summary of Product Characteristics of thalidomide for additional information.

Breast-feeding

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with bortezomib.

Fertility

Fertility studies were not conducted with bortezomib.

Effects on ability to drive and use machines

Bortezomib may have moderate influence on the ability to drive and use machines. Bortezomib may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines.

UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

Multiple myeloma

Undesirable effects were considered by the investigators to have at least a possible or probable causal relationship to bortezomib.

Overall, adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Post-marketing adverse reactions not seen in clinical studies are also included.

Table 7: Adverse reactions in patients with multiple myeloma treated with bortezomib in monotherapy or combination treatment.

System Organ Class	Incidence	Adverse Reaction
Infections and infestations	Common	Herpes zoster (incl disseminated & ophthalmic), Pneumonia, Herpes simplex, Fungal infection
	Uncommon	Infection, Bacterial infections, Viral infections, Sepsis (incl septic shock), Bronchopneumonia, Herpes virus infection, Meningoencephalitis herpetic, Bacteremia (incl staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection, Ear infection, Staphylococcal infection, Tooth infection
	Rare	Meningitis (incl bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukemia plasmacyte, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign
Blood and lymphatic system disorders	Very common	Thrombocytopenia, Neutropenia, Anemia
	Common	Leukopenia, Lymphopenia
	Uncommon	Pancytopenia, Febrile neutropenia, Coagulopathy, Leukocytosis, Lymphadenopathy, Hemolytic anemia
	Rare	Disseminated intravascular coagulation, Thrombocytosis, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (incl thrombocytopenic purpura), Blood disorder NOS, Hemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Angioedema, Hypersensitivity
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome, Hyperthyroidism, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration, Hypokalemia, Hyponatremia, Blood glucose abnormal, Hypocalcemia, Enzyme abnormality
	Uncommon	Tumor lysis syndrome, Failure to thrive, Hypomagnesaemia, Hypophosphatemia, Hyperkalemia, Hypercalcemia, Hypernatremia, Uric acid abnormal, Diabetes mellitus, Fluid retention
	Rare	Hypermagnesemia, Acidosis, Electrolyte imbalance, Fluid overload, Hypochloremia, Hypovolemia, Hyperchloremia, Hyperphosphatemia, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances, anxiety disorder, sleep disorders and disturbances
	Uncommon	Mental disorder, Hallucination, Psychotic disorder, Confusion, Restlessness
	Rare	Suicidal ideation, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very common	Neuropathies, Peripheral sensory neuropathy, Dysesthesia, Neuralgia
	Common	Motor neuropathy, Loss of consciousness (incl syncope), Dizziness, Dysgeusia, Lethargy, Headache
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia, Cerebellar coordination and balance disturbances, Memory loss (excl dementia), Encephalopathy, Posterior Reversible Encephalopathy Syndrome, Neurotoxicity, Seizure disorders, Post herpetic neuralgia, Speech disorder, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal, Parosmia
	Rare	Cerebral hemorrhage, Hemorrhage intracranial (incl subarachnoid), Brain edema, Transient ischemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy, Paralysis, Paresis, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia, Guillain Barre syndrome, Demyelinating polyneuropathy
Eye disorders	Common	Eye swelling, Vision abnormal, Conjunctivitis
	Uncommon	Eye hemorrhage, Eyelid infection, Chalazion, Blepharitis, Eye inflammation, Diplopia, Dry eye, Eye irritation, Eye pain, Lacrimation increased, Eye discharge
	Rare	Corneal lesion, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy, Different degrees of visual impairment (up to blindness)
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Dysacusis (incl tinnitus), Hearing impaired (up to and incl deafness), Ear discomfort
	Rare	Ear hemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade, Cardio-pulmonary arrest, Cardiac fibrillation (incl atrial), Cardiac failure (incl left and right ventricular), Arrhythmia, Tachycardia, Palpitations, Angina pectoris, Pericarditis (incl pericardial effusion), Cardiomyopathy, Ventricular dysfunction, Bradycardia
	Rare	Atrial flutter, Myocardial infarction, Atrioventricular block, Cardiovascular disorder (incl cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension, Orthostatic hypotension, Hypertension
	Uncommon	Cerebrovascular accident, Deep vein thrombosis, Hemorrhage, Thrombophlebitis (incl superficial), Circulatory collapse (incl hypovolemic shock), Phlebitis, Flushing, Hematoma (incl perirenal), Poor peripheral circulation, Vasculitis, Hyperemia (incl ocular)
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discoloration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnea, Epistaxis, Upper/lower respiratory tract infection, Cough
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (incl acute), Pulmonary alveolar hemorrhage, Bronchospasm, Chronic obstructive pulmonary disease, Hypoxemia, Respiratory tract congestion, Hypoxia, Pleurisy, Hiccups, Rhinorrhea, Dysphonia, Wheezing
	Rare	Respiratory failure, acute respiratory distress syndrome, Apnea, Pneumothorax, Atelectasis, Pulmonary hypertension, Hemoptysis, Hyperventilation, Orthopnea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, increased upper airway secretion, Throat irritation, Upper-airway cough syndrome
Gastrointestinal disorders	Very common	Nausea and vomiting symptoms, Diarrhea, Constipation
	Common	Gastrointestinal hemorrhage (incl mucosal), Dyspepsia, Stomatitis, Abdominal distension, Oropharyngeal pain, Abdominal pain (incl gastrointestinal and splenic pain), Oral disorder, Flatulence
	Uncommon	Pancreatitis (incl chronic), Hematemesis, Lip swelling, Gastrointestinal obstruction (incl small intestinal obstruction, ileus), Abdominal discomfort, Oral ulceration, Enteritis, Gastritis, Gingival bleeding, Gastroesophageal reflux disease, Colitis (incl clostridium difficile), Colitis ischemic, Gastrointestinal inflammation, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder, Salivary gland disorder
	Rare	Pancreatitis acute, Peritonitis, Tongue oedema, Ascites, Esophagitis, Cheilitis, Fecal incontinence, Anal sphincter atony, Fecaloma, Gastrointestinal ulceration and perforation, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal feces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality
	Uncommon	Hepatotoxicity (incl liver disorder), Hepatitis, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic hemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic hemorrhage, Cholelithiasis
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Dermatitis, Hair disorder, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer, Acne, Blister, Pigmentation disorder
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar plantar erythrodysesthesia syndrome, Hemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhea, Cold sweat, Skin disorder NOS, Erythroses, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis, Joint stiffness, Myopathies, Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations, Synovial cyst
Renal and urinary disorders	Common	Renal impairment
	Uncommon	Renal failure acute, Renal failure chronic, Urinary tract infection, Urinary tract signs and symptoms, Hematuria, Urinary retention, Micturition disorder, Proteinuria, Azotemia, Oliguria, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal hemorrhage, Genital pain, Erectile dysfunction,
	Rare	Testicular disorder, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, family and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very common	Pyrexia, Fatigue, Asthenia
	Common	Edema (incl peripheral), Chills, Pain, Malaise
	Uncommon	General physical health deterioration, Face edema, Injection site reaction, Mucosal disorder, Chest pain, Gait disturbance, feeling cold, Extravasation, Catheter related complication, change in thirst, Chest discomfort, Feeling of body temperature change, Injection site pain
	Rare	Death (incl sudden), Multi-organ failure, Injection site hemorrhage, Hernia(incl hiatus), Impaired healing, Inflammation, Injection site phlebitis, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinemia, Protein analyses abnormal, Weight increased, Blood test abnormal, C-reactive protein increased
	Rare	Blood gases abnormal, Electrocardiogram abnormalities (incl QT prolongation), International normalized ratio abnormal, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology, Urine analysis abnormal
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures, Rigors, Face injury, Joint injury, Burns, Laceration, Procedural pain, Radiation injuries
Surgical and medical procedures	Rare	Macrophage activation

Mantle cell lymphoma (MCL)

Additional identified adverse reactions associated with the use of Bortezomib combination therapy with rituximab, cyclophosphamide, doxorubicin, and prednisone were hepatitis B infection (<1%) and myocardial ischemia (1.3%).

Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the hematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions in patients with Mantle Cell Lymphoma treated with Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone

System Organ Class	Incidence	Adverse Reaction
Infections and infestations	Very common	Pneumonia
	Common	Sepsis (incl septic shock), Herpes zoster (incl disseminated & ophthalmic), Herpes virus infection, Bacterial infections, Upper/lower respiratory tract infection, Fungal infection, Herpes simplex
	Uncommon	Hepatitis B, Infection, Bronchopneumonia
Blood and lymphatic system disorders	Very common	Thrombocytopenia, Febrile neutropenia, Neutropenia, Leukopenia, Anemia, Lymphopenia
	Uncommon	Pancytopenia
Immune system disorders	Common	Hypersensitivity
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hypokalemia, Blood glucose abnormal, Hyponatremia, Diabetes mellitus, Fluid retention
	Uncommon	Tumor lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances
Nervous system disorders	Very common	Peripheral sensory neuropathy, Dysesthesia, Neuralgia
	Common	Neuropathies, Motor neuropathy, Loss of consciousness (incl syncope), Encephalopathy, Peripheral sensorimotor neuropathy, Dizziness, Dysgeusia, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal
Ear and labyrinth disorders	Common	Discuses (incl tinnitus)
	Uncommon	Vertigo, Hearing impaired (up to and incl deafness)
Cardiac disordes	Common	Cardiac fibrillation (incl atrial), Arrhythmia, Cardiac failure (incl left and right ventricular), Myocardial ischaemia, Ventricular dysfunction
	Uncommon	Cardiovascular disorder (incl cardiogenic shock)
Vascular disorders	Common	Hypertension, Hypotension, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnea, Cough, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (incl acute)
Gastrointestinal disorders	Very common	Nausea and vomiting symptoms, Diarrhea, Stomatitis, Constipation
	Common	Gastrointestinal hemorrhage (incl mucosal), Abdominal distension, Dyspepsia, Oropharyngeal pain, Gastritis, Oral ulceration, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation, Abdominal pain (incl gastrointestinal and splenic pain), Oral disorder
	Uncommon	Colitis (incl clostridium difficile)
Hepatobiliary disorders	Common	Hepatotoxicity (incl liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very common	Hair disorder
	Common	Pruritus, Dermatitis, Rash
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, Musculoskeletal pain, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection
General disorders and administration site conditions	Very common	Pyrexia, Fatigue, Asthenia
	Common	Oedema (incl peripheral), Chills, Injection site reaction, Malaise
Investigations	Common	Hyperbilirubinemia, Protein analyses abnormal, Weight decreased, Weight increased

OVERDOSE

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies.

There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored, and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature.

In the event of an overdose, go to the nearest hospital or contact the poison centers:

Hospital de Niños Dr. Ricardo Gutiérrez: Phone #: (011) 4962-9247/9248/9212
Hospital Pedro de Elizalde: Phone #: (011) 4300-2115 / 4362-6063
Hospital Dr. A. Posadas Phone #: (011) 4654-6648/ 4658-7777 / 0800-3330160
Hospital Dr. Juan A. Fernández: Phone #: (011) 4808-2655

STABILITY.

Unopened BORTMEX vials are stable until the date indicated on the container, if stored in the original container protected from light.

When reconstituted as directed, BORTMEX should be stored at room temperature. Reconstituted BORTMEX should be administered within eight hours of preparation. Reconstituted material may be stored in the original vial and/or syringe prior to administration. The product may be stored for up to three hours in a syringe, however, the total shelf life of the reconstituted material should not exceed 8 hours when exposed to artificial light.

PHARMACEUTICAL FORM

BORTMEX package containing 1 vial, 10 ml
Do not use this medicine after its expiry date

KEEP AT ROOM TEMPERATURE (15 °C TO 30 °C)
PROTECT FROM LIGHT IN ITS ORIGINAL PACKAGE

KEEP OUT OF THE REACH OF CHILDREN.

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH (ANMAT).
CERTIFICATE NO. 57,765

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