pharmaniaga®

# Retrox

**3.5 mg**

**Powder for Solution for Injection**
**(Bortezomib)**

**Name of The Medicine**

Retrox 3.5mg Powder for Solution for Injection

**Composition**

Each vial contains:

Active ingredient: 3.5 mg of bortezomib as a sterile lyophilized powder

Excipients:

Mannitol

**Product Description**

Before reconstitute: White to off white lyophilized powder/cake.

After reconstitution with 1.4 ml: 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

After reconstitution with 3.5 ml: 1 ml of solution for intravenous injection contains 1 mg bortezomib.

The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The compatible reconstitution and infusion solution for intravenous and subcutaneous use is 0.9% Sodium Chloride.

**Pharmacodynamics**

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG01.

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 signalling 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 tumourigenesis, 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.

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 tumour growth in vivo in many preclinical tumour models, including multiple myeloma.

Bortezomib 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.

**Pharmacokinetics**

Absorption

The mean first-dose maximum plasma concentrations of bortezomib were 57 and 112ng/mL, respectively following intravenous bolus administration of a 1.0 mg/m$^2$ and 1.3mg/m$^2$dose to patients with multiple myeloma. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m$^2$ dose and 89 to 120 ng/mL for the 1.3 mg/m$^2$ dose.

The total systemic exposure after repeat dose administration dose of 1.3mg/m$^2$ was equivalent for SC and IV administration. The Cmax after SC administration was lower than IV.

Distribution

The mean distribution volume (Vd) of bortezomib ranged from 1,659 l to 3,294 l following single- or repeated-dose intravenous administration of 1.0 mg/m$^2$ or 1.3 mg/m$^2$ to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. Over a bortezomib concentration range of 0.01 to 1.0 μg/ml, the *in vitro* protein binding averaged 82.9% in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.

Biotransformation

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 (t1/2) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m$^2$ and 1.3 mg/m$^2$, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m$^2$ and 1.3 mg/m$^2$, respectively.

Special populations

*Hepatic impairment*

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m$^2$.

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised 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 monitored closely.

*Renal impairment*

Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL≥60 mL/min/1.73 m$^2$), Mild (CrCL=40-59 mL/min/1.73m$^2$), Moderate (CrCL=20-39 mL/min/1.73 m$^2$), and Severe (CrCL<20 mL/min/1.73 m$^2$). A group of dialysis patients who were dosed after dialysis was also included. Patients were administered intravenous doses of 0.7 to 1.3 mg/m$^2$ of bortezomib twice weekly.

*Age*

The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m2 doses to pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Clearance of bortezomib increased with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

**Indication**

Bortezomib is indicated for the treatment of patients with multiple myeloma.

Bortezomib is indicated for the treatment of patients with mantle cell lymphoma.

**Recommended Dose**

Important Dosing Guidelines

Bortezomib is for intravenous or subcutaneous use only. Do not administer Bortezomib by any other route.

**Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered.**

The recommended starting dose of Bortezomib is 1.3 mg/m$^2$. Bortezomib may be administered intravenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5 mg/ml.

Bortezomib retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with bortezomib and who have relapsed at least 6 months after completing prior bortezomib treatment. Treatment may be started at the last tolerated dose.

When administered intravenously, administer Bortezomib as a 3 to 5 second bolus intravenous injection.

3295

**Bortezomib for Injection 3.5 mg/vial**

4503295

Dosage in Previously Untreated Multiple Myeloma

Bortezomib is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles as shown in **Table 1**. In Cycles 1 to 4, Bortezomib is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, Bortezomib is administered once weekly (Days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of Bortezomib.

**Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma**

| **Twice weekly Bortezomib (cycles 1 to 4)** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **1** | | | | **2** | | **3** | **4** | | **5** | | **6** |
| Bz (1.3 mg/m$^2$) | Day 1 | -- | -- | Day 4 | Day 8 | Day 11 | rest period | Day 22 | Day 25 | Day 29 | Day 32 | rest period |
| M (9 mg/m$^2$) P (60 mg/m$^2$) | Day 1 | Day 2 | Day 3 | Day 4 | -- | -- | rest period | -- | -- | -- | -- | rest period |
| **Once weekly Bortezomib (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)** | | | | | | | | | | | | |
| **Week** | **1** | | | | **2** | | **3** | **4** | | **5** | | **6** |
| Bz (1.3 mg/m$^2$) | Day 1 | -- | -- | -- | Day 8 | | rest period | Day 22 | | Day 29 | | rest period |
| M (9 mg/m$^2$) P (60 mg/m$^2$) | Day 1 | Day 2 | Day 3 | Day 4 | -- | -- | rest period | -- | -- | -- | -- | rest period |

Bz= Bortezomib; M=melphalan, P=prednisone

**Dose Modification Guidelines for Bortezomib when given in Combination with Melphalan and Prednisone**

Prior to initiating any cycle of therapy with Bortezomib in combination with melphalan and prednisone:

- Platelet counts should be at least 70 x 10$^9$/L and the absolute neutrophils count (ANC) should be at least 1.0 x 10$^9$/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline

**Table 2: Dose Modifications during Cycles of Combination Bortezomib, Melphalan and Prednisone Therapy**

| **Toxicity** | **Dose modification or delay** |
|---|---|
| Haematological 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 count is not above 30 × 10$^9$/L or ANC is not above 0.75 x 10$^9$/L on a Bortezomib dosing day (other than day 1) | Withhold Bortezomib dose |
| If several Bortezomib doses in consecutive cycles are withheld due to toxicity | Reduce Bortezomib dose by 1 dose level (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$) |
| Grade 3 or higher non-haematological toxicities | Withhold Bortezomib therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$). For Bortezomib -related neuropathic pain and/or peripheral neuropathy, hold or modify Bortezomib as outlined in **Table 6.** |

For information concerning melphalan and prednisone, see manufacturer's prescribing information.

Dose modifications guidelines for peripheral neuropathy are provided.

**Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)**

*Combination therapy with dexamethasone*

Bortezomib 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m$^2$ 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.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Four 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 via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m$^2$ body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in 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 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Bortezomib treatment cycle.

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 3).

Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

**Table 3: Posology for Bortezomib combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation**

| | | | | | |
|---|---|---|---|---|---|
| **Bz +Dx** | **Cycles 1 to 4** | | | | |
| | **Week** | **1** | **2** | **3** | |
| | Bz (1.3 mg/m$^2$) | 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** | **4** |
| | Bz (1.3 mg/m$^2$) | 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 | - | - |
| | **Cycles 2 to 4[b]** | | | | |
| | Bz (1.3 mg/m$^2$) | Day 1, 4 | Day 8, 11 | Rest Period | Rest Period |
| | T 200 mg[a] | 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.

**Dosage adjustments for transplant eligible patients**

For Bortezomib dosage adjustments, as described under "**Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma**" and "**Dose Modifications for Peripheral Neuropathy**" should be followed.

In addition, 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 according to the recommendations in the local package inserts.

**Dosage in Previously Untreated Mantle Cell Lymphoma**

Bortezomib (1.3 mg/m$^2$) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (BzR-CAP) for 6 three-week treatment cycles as shown in **Table 4**. Bortezomib is administered first followed by rituximab. Bortezomib is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period on Days 12 to 21. For patients with a response first documented at cycle 6, two additional BzR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of Bortezomib.

**Table 4: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma**

| **Twice weekly Bortezomib (6, Three Week Cycles)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Week** | **1** | | | | | **2** | | **3** |
| Bortezomib (1.3 mg/m$^2$) | Day 1 | -- | -- | Day 4 | -- | Day 8 | Day 11 | Rest period |
| Rituximab (375 mg/m$^2$) Cyclophosphamide (750mg/m$^2$) Doxorubicin (50 mg/m$^2$) | Day 1 | -- | -- | | | -- | -- | Rest period |
| Prednisone (100 mg/m$^2$) | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | -- | -- | Rest period |

* Dosing may continue for 2 more cycles (for a total of 8 cycles) if response is first seen at cycle 6.

**Dose Modification Guidelines for Bortezomib When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone**

Prior to the first day of each cycle (other than Cycle 1):

- Platelet counts should be at least 100 x 10$^9$/L and absolute neutrophil count (ANC) should be at least 1.5 x 10$^9$/L
- Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

Interrupt Bortezomib treatment at the onset of any Grade 3 hematologic or non-hematological toxicities, excluding neuropathy [**see Table 6** and **Special warnings and special precautions for use**]. For dose adjustments, see **Table 5** below.

**Table 5: Dose Modifications on Days 4, 8, and 11 during Cycles of Combination Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy**

| **Toxicity** | **Dose modification or delay** |
|---|---|
| Haematological toxicity | |
| Grade 3 or higher neutropenia, or a platelet count not at or above 25 x 10$^9$/L | Withhold Bortezomib therapy for up to 2 weeks until the patient has an ANC at or above 0.75 x 10$^9$/L and a platelet count at or above 25 x 10$^9$/L.<br>• If, after Bortezomib has been withheld, the toxicity does not resolve, discontinue Bortezomib.<br>• If toxicity resolves such that the patient has an ANC at or above 0.75 x 10$^9$/L and a platelet count at or above 25 x 10$^9$/L, Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$). |
| Grade 3 or higher non-hematological toxicities | Withhold Bortezomib therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$).<br>For Bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify Bortezomib as outlined in Table 6. |

For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.

**Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma**

Bortezomib (1.3 mg/m$^2$/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib.

Patients with multiple myeloma who have previously responded to treatment with Bortezomib (either alone or in combination) and who have relapsed at least six months after their prior Bortezomib therapy may be started on Bortezomib at the last tolerated dose. Retreated patients are administered Bortezomib twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Bortezomib. Bortezomib may be administered either as a single agent or in combination with dexamethasone.

Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below. Once the symptoms of the toxicity have resolved, Bortezomib therapy may be reinitiated at a 25% reduced dose (1.3 mg/m$^2$/dose reduced to 1 mg/m$^2$/dose; 1 mg/m$^2$/dose reduced to 0.7 mg/m$^2$/dose).

For dose modifications guidelines for peripheral neuropathy, see Dose modifications for peripheral neuropathy below.

**Dose Modifications for Peripheral Neuropathy**

Starting Bortezomib subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with Bortezomib only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during Bortezomib therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience Bortezomib-related neuropathic pain and/or peripheral neuropathy see **Table 6**.

**Table 6: Recommended Dose Modification for Bortezomib related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy**

| **Severity of Peripheral Neuropathy Signs and Symptoms*** | **Modification of Dose and Regimen** |
|---|---|
| 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 to 1.0 mg/m$^2$ |
| Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL***) | Withhold Bortezomib treatment until toxicity resolves. When toxicity resolves re-initiate with a reduced dose of bortezomib at 0.7 mg/m$^2$ once per week |
| Grade 4 (life-threatening consequences; urgent intervention indicated) | Discontinue bortezomib |

Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.

** Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.

*** Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

**Special Populations**

*Patients with Renal Impairment*

The pharmacokinetics of Bortezomib are not influenced by the degree of renal impairment. Therefore, dosing adjustments of Bortezomib are not necessary for patients with renal insufficiency. Since dialysis may reduce Bortezomib concentrations, the drug should be administered after the dialysis procedure.

*Patients with Hepatic Impairment*

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended Bortezomib dose. For patients with moderate or severe hepatic impairment, see **Table 7** below:

**Table 7: Recommended Starting Dose Modification for Bortezomib in Patients with Hepatic Impairment**

| | **Bilirubin level** | **SGOT (AST) Levels** | **Modification of Starting Dose in Multiple Myeloma and Relapsed Mantle Cell Lymphoma (1.3 mg/m$^2$ twice weekly)** |
|---|---|---|---|
| Mild | ≤ 1.0 x ULN | > ULN | None |
| | > 1.0 x −1.5 x ULN | Any | None |
| Moderate | > 1.5 x −3 x ULN | Any | Reduce Bortezomib to 0.7 mg/m$^2$ in the first treatment cycle. Consider dose escalation to 1.0 mg/m$^2$ or further dose reduction to 0.5 mg/m$^2$ in subsequent cycles based on patient tolerability. |
| Severe | > 3 x ULN | Any | |

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.

**Administration**

Bortezomib is administered intravenously or subcutaneously. When administered intravenously, Bortezomib is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection. For subcutaneous administration, the reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local injection site reactions occur following Bortezomib injection subcutaneously, a less concentrated Bortezomib solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously, or changed to IV injection

**Route of Administration**

For intravenous (IV) and subcutaneous (SC) use only

**Contraindication**

Hypersensitivity to the active substance, to boron or mannitol (E421) and of the excipients.

Acute diffuse infiltrative pulmonary and pericardial disease.

When bortezomib is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications.

**Warning and Precautions**

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 (see section Pregnancy and Lactation).

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib 1 mg powder for solution for injection is for intravenous use only, while 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, diarrhoea, vomiting and constipation are very common with bortezomib treatment. Cases of ileus have been uncommonly reported (see section Undesirable Effects). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). Patients with relapsed multiple myeloma treated with bortezomib and patients with previously untreated MCL treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BzR-CAP), one of the most common haematologic 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.

In patients with MCL, there was a higher incidence of Grade ≥ 3 thrombocytopenia in the bortezomib treatment group (BzR-CAP) as compared to the non- Bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]).

The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events as well as Grade 3 and higher bleeding events. In the BzR-CAP group, more patients received platelet transfusions compared to patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage, 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 (see section Recommended Dosage). 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 (see section Recommended Dose).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section Recommended Dose)

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with Bortezomib.

Patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with Bortezomib+Melphalan+Prednisone compared with Melphalan+Prednisone.

In patients with MCL, there was higher incidence of herpes zoster infection in the bortezomib treatment group (BzR-CAP) as compared to the non-Bortezomib treatment group (R-CHOP) (see section Undesirable Effect).

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. Refer to the Summary of Product Characteristics of rituximab for more information.

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.

Peripheral neuropathy

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, paraesthesia, discomfort, neuropathic pain or weakness.

Grade ≥ 2 and Grade ≥ 3 peripheral neuropathy occurred in the subcutaneous injection group was lower compared to the intravenous injection group.

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 (see section Recommended Dose). 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.

Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension

Bortezomib treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on bortezomib (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with bortezomib. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy.

Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving bortezomib. PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, bortezomib should be discontinued.

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, causality has not been established.

Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib (see section Undesirable Effects). Some of these events have been fatal. A pre-treatment

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chest radiograph 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, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing bortezomib therapy.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections Recommended Dose and Pharmacokinetics).

Hepatic impairment

Bortezomib is metabolised 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 (see sections Recommended Dose and Pharmacokinetics).

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, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section Undesirable Effect).

Tumour lysis syndrome

Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour 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 (see section Interaction with Other Medicaments).

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics (see section Interaction with Other Medicaments).

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 Medicaments**

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 metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

There was no significant effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously).

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.

There was no significant effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously).

The effect of melphalan-prednisone on the pharmacokinetics of Bortezomib (injected intravenously), is not considered clinically relevant.

Hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

**Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section Instruction for Use.

**Pregnancy and Lactation**

Contraception in males and females

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

Pregnancy

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

Bortezomib had no effects on embryonal/foetal 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. 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 foetus.

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 programme are met. Patients receiving Bortezomib in combination with thalidomide should adhere to the pregnancy prevention programme 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.

**Undesirable Effects**

Summary of the safety profile

Serious adverse reactions uncommonly reported during treatment with bortezomib include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions

*Multiple Myeloma*

*Table 7: Adverse reactions in patients with Multiple Myeloma treated with Bortezomib*

| System Organ Class | Incidence | Adverse reaction |
|---|---|---|
| Infections and infestations | Common | Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection* |
| | Uncommon | Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic#, Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection* |
| | Rare | Meningitis (inc 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, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign* |
| Blood and lymphatic system disorders | Very Common | Thrombocytopenia*, Neutropenia*, Anaemia* |
| | Common | Leukopenia*, Lymphopenia* |
| | Uncommon | Pancytopenia*, Febrile neutropenia, Coagulopathy#, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia# |
| | Rare | Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (including Thrombocytopenic purpura), Blood disorder NOS, Haemorrhagic 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, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality* |
| | Uncommon | Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention |
| | Rare | Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, 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, Dysaesthesia*, Neuralgia* |
| | Common | Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache* |
| | Uncommon | Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc 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 haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic 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 haemorrhage*, 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 (inc tinnitus)*,Hearing impaired (up to and inc deafness), Ear discomfort* |
| | Rare | Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS |
| Cardiac disorders | Uncommon | Cardiac tamponade#, Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia |
| | Rare | Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc 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*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)* |
| | Rare | Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency |
| Respiratory, thoracic and mediastinal disorders | Common | Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough* |
| | Uncommon | Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage#, Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing |
| | Rare | Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, 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*, Diarrhoea*, Constipation |
| | Common | Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence |
| | Uncommon | Pancreatitis (inc chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic#, Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder* |
| | Rare | Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces |
| Hepatobiliary disorders | Common | Hepatic enzyme abnormality* |
| | Uncommon | Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis |
| | Rare | Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis |
| Skin and subcutaneous tissue disorders | Common | Rash*, Pruritus*, Erythema, Dry skin |
| | 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 erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, 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*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria |
| | Rare | Bladder irritation |
| Reproductive system and breast disorders | Uncommon | Vaginal haemorrhage, Genital pain*, Erectile dysfunction, |
| | Rare | Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration |
| Congenital, familial and genetic disorders | Rare | Aplasia, Gastrointestinal malformation, Ichthyosis |
| General disorders and administration site conditions | Very Common | Pyrexia*, Fatigue, Asthenia |
| | Common | Oedema (inc peripheral), Chills, Pain*, Malaise* |
| | Uncommon | General physical health deterioration*, Face oedema*, 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 (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia (inc 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 | Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*, C-reactive protein increased |
| | Rare | Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised 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 |

NOS=not otherwise specified
* Grouping of more than one MedDRA preferred term.
# Postmarketing adverse reaction

*Table 8 Adverse reactions in patients with Mantle Cell Lymphoma treated with BzR -CAP*

| System Organ Class | Incidence | Adverse reaction |
|---|---|---|
| Infections and infestations | Very Common | Pneumonia* |
| | Common | Sepsis (inc septic shock)*, Herpes zoster (inc 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*, Anaemia*, Lymphopenia* |
| | Uncommon | Pancytopenia* |
| Immune system disorders | Common | Hypersensitivity* |
| | Uncommon | Anaphylactic reaction |
| Metabolism and nutrition disorders | Very Common | Decreased appetite |
| | Common | Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention |
| | Uncommon | Tumour lysis syndrome |
| Psychiatric disorders | Common | Sleep disorders and disturbances* |
| Nervous system disorders | Very Common | Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia* |
| | Common | Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy |
| | Uncommon | Autonomic nervous system imbalance |
| Eye disorders | Common | Vision abnormal* |
| Ear and labyrinth disorders | Common | Dysacusis (inc tinnitus)* |
| | Uncommon | Vertigo*, Hearing impaired (up to and inc deafness) |
| Cardiac disorders | Common | Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction* |
| | Uncommon | Cardiovascular disorder (inc cardiogenic shock) |
| Vascular disorders | Common | Hypertension*, Hypotension*, Orthostatic hypotension |
| Respiratory, thoracic and mediastinal disorders | Common | Dyspnoea*, Cough*, Hiccups |
| | Uncommon | Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute) |
| Gastrointestinal disorders | Very Common | Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation |
| | Common | Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder* |
| | Uncommon | Colitis (inc clostridium difficile)* |
| Hepatobiliary disorders | Common | Hepatotoxicity (inc 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 (inc peripheral), Chills, Injection site reaction*, Malaise* |
| Investigations | Common | Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased |

* Grouping of more than one MedDRA preferred term.

**Symptoms and Treatment of 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. 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 (see sections Recommended Dosage and Warning and Precautions).

**Effect on Ability to Drive and Use Machine**

Bortezomib may have a 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 and should be advised not to drive or operate machinery if they experience these symptoms (see section Side Effect).

**Instructions for Use**

General Precautions

Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Bortezomib. Use of gloves and other protective clothing to prevent skin contact is recommended.

**Aseptic technique** must be strictly observed throughout the handling of bortezomib, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib 1 mg powder for solution for injection is for intravenous use only, while Bortezomib 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.

Instructions for reconstitution

Bortezomib must be reconstituted by a healthcare professional.

*Intravenous injection*

Each 10 ml vial of bortezomib must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

*Subcutaneous injection*

Each 10 ml vial of bortezomib must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal

Bortezomib is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Storage Condition**

**Store below 30°C.**

Keep the vial in the outer carton in order to protect from light.

The total storage time for the reconstituted medicinal product should be not more than 8 hours at 25°C prior to administration.

**Shelf Life**

Unopened vial

2 years

Reconstituted solution

The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should be not more than 8 hours at 25°C prior to administration.

**PACKAGING**

1 x 10mL vial of Bortezomib Powder for Solution for Injection (Lyophilised Powder). 1 vial packed in mono carton.

**ATC CODE**

ATC Code: L01XG01

**MANUFACTURER**

Shilpa Medicare Limited,

Unit IV, Plot No. S-20 to S-26, Pharma SEZ, TSIIC, Green Industrial Park,

Polepally Village, Jadcherla Mandal, Mahabubnagar-District, 509301 Telangana India.

**PRODUCT REGISTRATION HOLDER**

InspiraPharma Sdn Bhd

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08000 Sungai Petani, Kedah Darul Aman, Malaysia

**DATE OF REVISION**

27 Jan 2026

**PRODUCT REGISTRATION NUMBER**

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