Package insert

1 NAME OF THE MEDICINAL PRODUCT

BortiRel (Bortezomib 3.5 mg powder for solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg bortezomib
After reconstitution, each ml of solution for intravenous injection contains 1 mg bortezomib.
After reconstitution, each ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

3 PHARMACEUTICAL FORM

White to off white lyophilized powder or cake. BortiRel (Bortezomib 3.5 mg powder for solution for injection) should be reconstituted with 0.9% Sodium Chloride before administration. No accompanying diluent is provided.

Description of reconstitution solution
A clear, colorless solution should be free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BortiRel is indicated for the treatment of patients with multiple myeloma.
BortiRel is indicated for the treatment of patients with mantle cell lymphoma.

4.2 Posology and method of administration

Recommended dose
Important Dosing Guidelines
BortiRel 3.5mg is for intravenous or subcutaneous use only. Do not administer BortiRel 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 BortiRel is 1.3 mg/m^2. BortiRel may be administered intravenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5 mg/ml.

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

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

Dosage in Previously Untreated Multiple Myeloma
BortiRel is administered in combination with oral mephalan and oral prednisone for nine 6-week treatment cycles as shown in **Table 1**. In Cycles 1-4, BortiRel is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, BortiRel is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of BortiRel.

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

Twice Weekly BortiRel (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
BortiRel (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
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once Weekly BortiRel (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
BortiRel (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Dose Modification Guidelines for BortiRel when given in Combination with Melphalan and Prednisone:
Prior to initiating any cycle of therapy with BortiRel in combination with melphalan and prednisone:

- Platelet count should be at least 70 x 10^9/L and the absolute neutrophil count (ANC) should be at least 1 x 10^9/L;
- Nonhematological toxicities should have resolved to Grade 1 or baseline.

Table 2: Dose modifications during cycles of combination of BortiRel, Melphalan and Prednisone therapy.

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 count is not above 30 × 10^9/L or ANC is not above 0.75 x 10^9/L on a BortiRel dosing day (other than day 1)	Withhold BortiRel dose
If several BortiRel doses in consecutive cycles are withheld due to toxicity	Reduce BortiRel 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-hematological toxicities	Withhold BortiRel therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, BortiRel 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 BortiRel-related neuropathic pain and/or peripheral neuropathy, hold or modify BortiRel 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
BortiRel 3.5mg 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 BortiRel. Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the BortiRel treatment cycle. Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide
BortiRel 3.5mg 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 BortiRel. Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the BortiRel 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 BortiRel combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

Vc+ Dx		**Cycles 1 to 4**			
	Week	**1**	**2**	**3**	
	Vc (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	-	
Vc+Dx+T		**Cycle 1**			
	Week	**1**	**2**	**3**	**4**
	Vc (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]			
	Vc (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	-	-

Vc= BortiRel; 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 BortiRel 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 BortiRel 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
BortiRel (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6 three week treatment cycles as shown in **Table 4**. BortiRel is administered first followed by rituximab. BortiRel 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 VcR- CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of BortiRel.

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

Twice Weekly BortiRel (6, Three Week Cycles) *								
Week	**1**					**2**		**3**
BortiRel (1.3 mg/m^2)	Day 1	--	--	Day 4	--	Day 8	Day 11	Rest period
Rituximab (375 mg/m^2) Cyclophosphamide (750 mg/m^2)	Day 1	--	--			--	--	Rest period

Doxorubicin (50 mg/m)								
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 BortiRel When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

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

- Platelet count 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 BortiRel treatment at the onset of any Grade 3 hematologic or nonhematological toxicities, excluding neuropathy [see **Table 6**]. For dose adjustments, see **Table 5** below.

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

Toxicity	**Dose modification or delay**
Hematological toxicity Grade 3 or higher neutropenia, or a platelet count not at or above 25 x 10^9/L	Withhold BortiRel 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. If, after BortiRel has been withheld, the toxicity does not resolve, discontinue BortiRel. 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, BortiRel 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 BortiRel therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, BortiRel 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 BortiRel related neuropathic pain and/or peripheral neuropathy, hold or modify BortiRel 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:

BortiRel (1.3 mg/m^2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a tenday rest period (Days 12 to 21). For extended therapy of more than eight cycles, BortiRel 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 BortiRel.

Patients with multiple myeloma who have previously responded to treatment with BortiRel (either alone or in combination) and who have relapsed at least six months after their prior BortiRel therapy may be started on BortiRel at the last tolerated dose. Retreated patients are administered BortiRel 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 BortiRel. BortiRel may be administered either as a single agent or in combination with dexamethasone.

BortiRel 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, BortiRel therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 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 BortiRel 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 BortiRel only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during BortiRel 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 BortiRel-related neuropathic pain and/or peripheral neuropathy see **Table 6**.

Table 6: Recommended dose modification for BortiRel-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 paresthesias) 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 BortiRel to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold BortiRel therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BortiRel at 0.7 mg/m^2 once per week.
Grade 4 (life- threatening consequences; urgent intervention indicated)	Discontinue BortiRel

*Grading based on NCI Common Toxicity Criteria CTCAE v4.0.
**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 medications, and not bedridden

Special populations
Patients with Renal Impairment
The pharmacokinetics of BortiRel are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BortiRel are not necessary for patients with renal insufficiency. Since dialysis may reduce BortiRel 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 BortiRel dose. For patients with moderate or severe hepatic impairment, see **Table 7** below.

Table 7: Recommended starting dose modification for BortiRel 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	≤ 1.0x ULN	> ULN	None
	> 1.0x-1.5x ULN	Any	None
Moderate	> 1.5x-3x ULN	Any	Reduce BortiRel to 0.7 mg/m^2 in the first 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
Severe	> 3x ULN	Any	

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

Administration
BortiRel 3.5mg is administered intravenously or subcutaneously. When administered intravenously, BortiRel 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 BortiRel injection subcutaneously, a less concentrated BortiRel solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously, or changed to IV injection.

Route of Administration
Intravenous or subcutaneously

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients.
Acute diffuse infiltrative pulmonary and pericardial disease.
When BortiRel is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications.

4.4 Special warnings and precautions for use

Bortirel should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

There have been fatal cases of inadvertent intrathecal administration of Bortezomib. Bortirel is for IV and subcutaneous use only. DO NOT ADMINISTER BORTIREL INTRATHECALLY.

When BortiRel 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 BortiRel. 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. Bortirel 1 mg powder for solution for injection is for intravenous use only, while Bortirel 3.5 mg powder for solution for injection powder for solution for injection is for intravenous or subcutaneous use. BortiRel 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.
Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity
Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). 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 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. 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.

In patients with MCL (study LYM-3002), there was a higher incidence (56.7% versus 5.8%) 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 [RCHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the BzR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (BzRCAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the BzR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of 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. 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 BortiRel. 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. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the BzR-CAP arm and 61% of patients in the R-CHOP arm. 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.

Herpes zoster virus reactivation
Antiviral prophylaxis is recommended in patients being treated with BortiRel. In the Phase III study in 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 (14% versus 4% respectively).
In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the BzR-CAP arm and 1.2% in the R-CHOP arm.

Hepatitis B Virus (HBV) reactivation and infection
When rituximab is used in combination with BortiRel, 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 BortiRel. 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 BortiRel 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.

In the Phase III study comparing bortezomib administered intravenously versus subcutaneously, the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for the subcutaneous injection group and 41% for the intravenous injection group (p=0.0124). Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 16% in the intravenous treatment group (p=0.0264). The incidence of all grade peripheral neuropathy with bortezomib administered intravenously was lower in the historical studies with bortezomib administered intravenously than in study MMY-3021.

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 BortiRel 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, BortiRel 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 in clinical studies, 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. Some of these events have been fatal. A pre-treatment 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 BortiRel therapy.

In a clinical trial, two patients (out of 2) given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and Bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 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 metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with BortiRel 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, hyperbilirubinaemia and hepatitis. Such changes may be reversible upon discontinuation of Bortezomib.

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. 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.

4.5 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 metaboliser 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), there was no significant effect on the pharmacokinetics of Bortezomib based on data from 17 patients.

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.

In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of Bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of Bortezomib based on data from 7 patients.

A drug-drug interaction study assessing the effect of melphalan-prednisone on the pharmacokinetics of Bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 17% based on data from 21 patients. This is not considered clinically relevant.

During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving BortiRel treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

4.6 Fertility, 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 clinical data are available for Bortezomib l with regard to exposure during pregnancy. The teratogenic potential of Bortezomib has not been fully investigated.

In non-clinical studies, 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. BortiRel should not be used during pregnancy unless the clinical condition of the woman requires treatment with BortiRel. If BortiRel 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 program are met. Patients receiving BortiRel 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 reaction in breast-fed infants, breast-feeding should be discontinued during treatment with BortiRel.

Fertility
Fertility studies were not conducted with Bortezomib.

4.7 Effects on ability to drive and use machines

BortiRel may have a moderate influence on the ability to drive and use machines. BortiRel 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 symptom.

4.8 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 list of adverse reactions
Multiple Myeloma
Undesirable effects in **Table 8** were considered by the investigators to have at least a possible or probable causal relationship to Bortezomib. These adverse reactions are based on an integrated data set of 5,476 patients of whom 3,996 were treated with Bortezomib at 1.3 mg/m^2 and included in Table 7. Overall, Bortezomib was administered for the treatment of multiple myeloma in 3,974 patients.

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. Table 8 has been generated using Version 14.1 of the MedDRA.

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

Table 8: Adverse reactions in patients with Multiple Myeloma treated with Bortezomib in clinical trials, and all post-marketing adverse reactions regardless of indication[#]

System Organ Class	Incidence	Adverse
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 (inc. 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-Barré 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, Palmarplantar 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.
# Post-marketing adverse reaction regardless of indication

Mantle Cell Lymphoma (MCL)
The safety profile of Bortezomib in 240 MCL patients treated with bortezomib at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BzR-CAP), versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (BzR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to Bortezomib alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the BzR-CAP arm and with at least a possible or probable causal relationship to the components of the BzR-CAP arm, are listed in Table 9 below. Also included are adverse drug reactions identified in the BzR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to bortezomib based on historical data in the multiple myeloma studies.

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. Table 9 has been generated using Version 16 of the MedDRA.

Table 9: Adverse reactions in patients with Mantle Cell Lymphoma treated with BzR-CAP in a clinical trial

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*
	Common	Dysacusis (inc tinnitus)*

Ear and labyrinth disorders	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.

Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the Bz+M+P arm.

The incidence of herpes zoster among patients in the Bz+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the BzR-CAP arm. The incidence of herpes zoster among patients in the BzR-CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis.

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n=1) of patients receiving Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BzRCAP). The overall incidence of hepatitis B infections was similar in patients treated with BzR-CAP or with R-CHOP (0.8% vs 1.2% respectively).

Peripheral neuropathy in combination regimens
Multiple Myeloma
In trials in which Bortezomib was administered as induction treatment in combination with dexamethasone (study IFM-2005-01), and dexamethasone-thalidomide (study MMY-3010), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 10: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		MMY-3010	
	VDDx (N=239)	BzDx (N=239)	TDx (N=126)	BzTDx (N=130)
Incidence of PN (%)				
All Grade PN	3	15	12	45
≥ Grade 2 PN	1	10	2	31
≥ Grade 3 PN	< 1	5	0	5
Discontinuation due to PN (%)	< 1	2	1	5

VDDx=vincristine, doxorubicin, dexamethasone; BzDx= Bortezomib, dexamethasone; TDx=thalidomide, dexamethasone; BzTDx= Bortezomib, thalidomide, dexamethasone; PN=peripheral neuropathy
Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma
In study LYM-3002 in which Bortezomib was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 11: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	BzR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%) All Grade PN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

BzR-CAP= Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone; RCHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PN=peripheral neuropathy
Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients
42.9% and 10.4% of patients in the BzR-CAP arm were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both BzR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the BzR-CAP groups was 68%, compared to 42% in the R-CHOP group.

Notable differences in the safety profile of Bortezomib administered subcutaneously versus intravenously as single agent
In the Phase III study patients who received Bortezomib subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity, and a 5% lower incidence of discontinuation of Bortezomib. The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were 12%-15% lower in the subcutaneous group than in the intravenous group. In addition, the incidence of Grade 3 or higher

peripheral neuropathies was 10% lower, and the discontinuation rate due to peripheral neuropathies 8% lower for the subcutaneous group as compared to the intravenous group.

Six percent of patients had an adverse local reaction to subcutaneous administration, mostly redness. Cases resolved in a median of 6 days, dose modification was required in two patients. Two (1%) of the patients had severe reactions; 1 case of pruritus and 1 case of redness.
The incidence of death on treatment was 5% in the subcutaneous treatment group and 7% in the intravenous treatment group. Incidence of death from "Progressive disease" was 18% in the subcutaneous group and 9% in the intravenous group.

Retreatment of patients with relapsed multiple myeloma
In a study in which Bortezomib retreatment was administered in 130 patients with relapsed multiple myeloma, who previously had at least partial response on a bortezomib-containing regimen, the most common all-grade adverse events occurring in at least 25% of patients were thrombocytopenia (55%), neuropathy (40%), anaemia (37%), diarrhoea (35%), and constipation (28%). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40% and 8.5% of patients, respectively.

4.9 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.

5.1 Pharmacodynamic properties

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 1500- 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 $t_{½}$ 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.

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 tumour growth in vivo in many preclinical tumour 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.

5.2 Pharmacokinetic properties

Absorption
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to 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/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients with multiple myeloma (in intravenous and subcutaneous group), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. The C_{max} after subcutaneous administration (20.4 ng/ml) was lower than intravenous (223 ng/ml). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18%-122.80%.

Distribution
The mean distribution volume (V_d) of Bortezomib ranged from 1659 l to 3294 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
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 ($t_{1/2}$) 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 during the first treatment cycle, including 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-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
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 m^2,), Mild (CrCL = 40-59 ml/min/1.73 m^2), Moderate (CrCL = 20-39 ml/min/1.73 m^2), and Severe (CrCL < 20 ml/min/1.73 m^2). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of Bortezomib twice weekly. Exposure of Bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups.

Age
The pharmacokinetics of Bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid

leukemia (AML). Based on a population pharmacokinetic analysis, clearance of Bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 L/hr/m^2, volume of distribution at steady- state was 834 L/m^2, and the elimination half-life was 100 hours. 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.

6 PHARMACEUTICAL PARTICULARS

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in **'Special precautions for disposal and other handling'**

Shelf Life:
Unopened Vials: 24 months

Reconstituted solution: The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Storage
Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

Reconstituted solution: The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Reconstituted Solution:
INTRAVENOUS INJECTION ONLY
Reconstitute with 3.5 ml of sterile (0.9% w/v) Sodium Chloride solution for Injection to make final concentration 1 mg/ml

SUBCUTANEOUS INJECTION ONLY
Reconstitute with 1.4 ml of sterile (0.9% w/v) Sodium Chloride solution for Injection to make final concentration 2.5 mg/ml

Packaging available
10 ml clear tubular USP type I siliconized blow back glass vials, stoppered with 20mm chlorobutyl double slotted rubber stopper and 20mm aluminium flip off seal with plastic button [dark grey].

Pack sizes: 1 box containing 1 single-use vial and leaflet.

Manufacturer
Reliance Life Sciences Pvt. Ltd. (Plant 6)
Dhirubhai Ambani Life Science Centre (DALC), Thane - Belapur Road, Rabale, Navi Mumbai, Maharashtra, IN-400701, India.

Product Registration Holder
Mansa Healthcare Sdn. Bhd.
B-05-3A, 3 Two Square, No 2, Jalan 19/1, 46300 Petaling Jaya, Selangor.

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*(*font size will be at least min size: 7, as measure in Times New Roman)*