SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Bortezomib Equity, 3,5 mg Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3,5 mg bortezomib (as a mannitol boronic ester).

After reconstitution, 1 mL of solution for **intravenous** injection contains 1 mg bortezomib.

After reconstitution, 1 mL of solution for **subcutaneous** injection contains 2,5 mg bortezomib.

Contains sugar. Each vial contains 35 mg mannitol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bortezomib Equity for injection is indicated for:

Multiple Myeloma

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation;
- in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with

haematopoietic stem cell transplantation;

- in combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high dose chemotherapy with haematopoietic stem cell transplantation.

Mantle Cell Lymphoma

- treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.
- treatment for newly diagnosed mantle cell lymphoma (MCL) in adults, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Posology

Bortezomib Equity 3,5 mg powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg/mL (as a 3-5 second bolus injection) or
- subcutaneous administration at a concentration 2,5 mg/mL.

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

BORTEZOMIB EQUITY IS FOR INTRAVENOUS AND SUBCUTANEOUS USE ONLY and should not be given by other routes. **Intrathecal administration has resulted in death.**

Bortezomib Equity retreatment may be considered for multiple myeloma patients who had previously responded to treatment with Bortezomib Equity (see below).

Monotherapy

Relapsed multiple myeloma and relapsed mantle cell lymphoma

Recommended dosage

The recommended starting dose of Bortezomib Equity is 1,3 mg/m^2 body surface area twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Bortezomib Equity.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of Bortezomib Equity beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of Bortezomib Equity therapy.

Dose modification and re-initiation of treatment

Bortezomib Equity treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see section 4.4). Once the symptoms of the toxicity have resolved, Bortezomib Equity treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2; 1,0 mg/m^2 reduced to 0,7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of Bortezomib Equity must be considered.

Patients who experience Bortezomib Equity related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 1. Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Caution should be used with Bortezomib Equity in patients with pre-existing severe neuropathy.

Table 1: Recommended* dose modifications for Bortezomib Equity related neuropathic pain and/or peripheral sensory neuropathy or motor neuropathy.

Severity of peripheral neuropathy **Signs and Symptoms** [a]	Modification of dose and regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia without pain or loss of function)	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting Instrumental Activities of Daily Living (ADL)) [b]	Reduce Bortezomib Equity to 1,0 mg/m^2 OR

	Change Bortezomib Equity treatment schedule to 1,3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL [c])	Withhold Bortezomib Equity treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate Bortezomib Equity treatment and reduce dose to 0,7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue Bortezomib Equity

*Based on dose modifications in phase II and III multiple myeloma studies

[a] Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

[b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money or other such daily activities.

[c] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using toilet, taking medications, and not bedridden.

Combination therapy

Previously untreated multiple myeloma – patients who are not eligible for stem cell transplantation

Recommended dosage in combination with melphalan and prednisone

Bortezomib Equity (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2. In Cycles 1-4, Bortezomib Equity is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Bortezomib Equity is administered once weekly (days 1, 8, 22 and 29).

Table 2: Recommended dosage regimen for Bortezomib Equity when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma who are not eligible for stem cell transplantation

Twice Weekly Bortezomib Equity (Cycles 1-4)						
Week	1	2	3	4	5	6

Vc (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 Equity (Cycles 5-9)												
Week	1				2	3	4		5		6	
Vc (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	

Vc = Bortezomib Equity; m = melphalan, p = prednisone

Dose management guidelines for combination therapy with melphalan and prednisone

Dose modification and re-initiation of therapy when Bortezomib Equity is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/L and the absolute neutrophil count (ANC) should be ≥ 1,0 x 10^9/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Dose modifications during subsequent cycles

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopaenia, or thrombocytopaenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.

• If platelet count ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a Bortezomib Equity dosing day (other than day 1)	Bortezomib Equity dose should be withheld.
• If several Bortezomib Equity doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib Equity 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 non-haematological toxicities	Bortezomib Equity therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib Equity 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 Equity-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib Equity as outlined in Table 1.

For additional information concerning melphalan and prednisone, refer to the respective professional information.

Previously untreated multiple myeloma – patients who are eligible for stem cell transplantation

Recommended dosage

The recommended starting dose of Bortezomib Equity in combination with other medicines used for the treatment of multiple myeloma is 1,3 mg/m^2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10-18 days, which is considered a treatment cycle. Three to six cycles should be administered. At least 72 hours should elapse between consecutive doses of Bortezomib Equity.

For Bortezomib Equity dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (Table 1) above.

For dosing instructions for other medicines combined with Bortezomib Equity, see their respective professional information.

Relapsed multiple myeloma

Recommended dosage in combination with pegylated liposomal doxorubicin

For Bortezomib Equity dosage and modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the Bortezomib Equity 3-week regimen as a 1-hour intravenous infusion administered after the Bortezomib Equity injection. For additional information concerning pegylated liposomal doxorubicin, see respective professional information.

Recommended dosage in combination with dexamethasone

For Bortezomib Equity dosage and modifications, see Monotherapy.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, Bortezomib Equity administration.

For additional information concerning dexamethasone, see respective professional information.

Retreatment for multiple myeloma

Patients who have previously responded to treatment with Bortezomib Equity (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to Monotherapy for dosing schedule.

Previously untreated mantle cell lymphoma

Recommended dosage in combination with rituximab, cyclophosphamide, doxorubicin and prednisone

For Bortezomib Equity dosage, see Monotherapy. Six Bortezomib Equity cycles are administered. For patients with a response first documented at Cycle 6, two additional Bortezomib Equity cycles are recommended.

The following medicines are administered on Day 1 of each Bortezomib Equity 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, and doxorubicin at 50 mg/m^2. Prednisone is administered orally at 100 mg/m^2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

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

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

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1,5 x 10^9/L
- Haemoglobin should be ≥ 8 g/dL (≥ 4,96 mmol/L)

- Non-haematologic toxicity should have recovered to Grade 1 or baseline

Bortezomib Equity treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 3 haematological toxicities, excluding neuropathy (see also section 4.4). For dose adjustments, see Table 4 below.

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. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 4: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity • ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x 10^9/L	Bortezomib Equity therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L. • If, after Bortezomib Equity has been held, the toxicity does not resolve, as defined above, then Bortezomib Equity must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, Bortezomib Equity dose should be reduced by one 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).
• if platelet count < 25 x 10^9/L or ANC < 0,75 x 10^9/L on a Bortezomib Equity day (other than Day 1)	Bortezomib Equity dose should be withheld.
Grade ≥ 3 non-haematological toxicities	Bortezomib Equity therapy should be withheld until

	symptoms of the toxicity have resolved to Grade 2 or better. Then, Bortezomib Equity 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 Equity-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib Equity as outlined in Table 1.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see the respective professional information.

Special populations

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (older than 65 years) with multiple myeloma or with mantle cell lymphoma (see section 4.8).

Patients with renal impairment

The pharmacokinetics of Bortezomib Equity are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance (CrCl) > 20 mL/min/1,73 m^2). Therefore, dosing adjustments of Bortezomib Equity are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce Bortezomib Equity concentrations, Bortezomib Equity should be administered after the dialysis procedure (see section 5.2).

Patients with hepatic impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended Bortezomib Equity dose. Patients with moderate or severe hepatic impairment should be started on Bortezomib Equity at a reduced dose of 0,7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see Table 5).

Table 5: Recommended starting dose modification for Bortezomib Equity in patients with hepatic

impairment

Grade of hepatic impairment*	**Bilirubin Level**	**SGOT (AST) Levels**	**Modification of starting dose**
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 Equity 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 tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

AST = aspartate aminotransferase, ULN = upper limit of the normal range.

* Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Paediatric patients

Bortezomib Equity has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data become available.

Method of administration

Treatment must be initiated and administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicine.

Administration precautions

There have been fatal cases of inadvertent intrathecal administration of Bortezomib Equity.

DO NOT ADMINISTER BORTEZOMIB EQUITY INTRATHECALLY.

Intravenous injection

The reconstituted solution 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.

At least 72 hours should elapse between consecutive doses of Bortezomib Equity.

Subcutaneous injection

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 Equity injection subcutaneously, a less concentrated Bortezomib Equity solution (1 mg/mL instead of 2,5 mg/mL) may be administered subcutaneously or changed to IV injection.

See section 6.6 for reconstitution instructions.

4.3 Contraindications

Hypersensitivity to bortezomib, to boron or to any of the excipients listed in section 6.1.

Acute diffuse infiltrative pulmonary and pericardial disease.

When Bortezomib Equity is given in combination with other medicines, refer to their Professional Information for additional contraindications.

4.4 Special warnings and precautions for use

There have been fatal cases of inadvertent intrathecal administration of Bortezomib Equity. Bortezomib Equity 3,5 mg is for IV or SC use.

DO NOT ADMINISTER BORTEZOMIB EQUITY INTRATHECALLY.

When Bortezomib Equity is given in combination with other medicines, the Professional Information of these other medicines must be consulted prior to initiation of treatment with bortezomib. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed.

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are frequently associated with

bortezomib treatment. Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of anti-emetics and anti-diarrhetic medicine Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity

Bortezomib treatment is frequently associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is a less frequent undesirable effect. The most frequent haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease and recovery remained consistent in studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied. The mean platelet count nadir measured was approximately 40 % of baseline.

Severe bleeding, including CNS and gastrointestinal bleeding, associated with thrombocytopenia, have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib. Bortezomib Equity 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 4.2 and 4.8). Bortezomib Equity should be used with caution particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Full blood counts (FBC) with differential and including platelet counts should be frequently monitored throughout treatment with Bortezomib Equity. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with Bortezomib Equity. In patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation has been reported as

more frequent in patients treated with bortezomib in combination with melphalan and prednisone, compared with when this medicine combination was given without bortezomib.

It has also been reported that the incidence of herpes zoster infection was higher when bortezomib was given in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, compared with when this medicine combination was given without bortezomib.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with Bortezomib Equity, 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, as in Bortezomib Equity. Antiviral prophylaxis should be considered. Refer to the Professional Information of rituximab for more information.

Laboratory tests

Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with Bortezomib Equity.

Progressive multifocal leukoencephalopathy (PML)

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 Equity if PML is diagnosed.

Peripheral neuropathy

Treatment with bortezomib causes a peripheral neuropathy which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported.

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with Bortezomib Equity. 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. The incidence of Grade ≥ 2 and Grade ≥ 3 peripheral neuropathy events was reported to be higher when bortezomib was given intravenously compared to being given subcutaneously. Therefore, patients with pre-existing peripheral neuropathy or at high risk of peripheral neuropathy may benefit from starting Bortezomib Equity subcutaneously.

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 4.2). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible. Improvement in, or resolution of, peripheral neuropathy has been reported in some patients with ≥ Grade 2 peripheral neuropathy.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving Bortezomib Equity in combination with medicines 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 less frequently 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 frequently 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 Equity or Bortezomib Equity may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines 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 medicines, 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 Equity should be discontinued. The safety of reinitiating Bortezomib Equity therapy in patients previously experiencing PRES is not known.

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. Patients using angiotensin inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during Bortezomib Equity treatment.

Electrocardiogram investigations

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

Pulmonary disorders

There have been 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 4.8). 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. Caution should be used prior to continuing Bortezomib Equity 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, administration with high doses cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours in combination with daunorubicin and bortezomib is not recommended.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections 4.2 and 5.2).

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 Equity at reduced doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatic reactions

Cases of acute hepatic failure have been reported in patients receiving bortezomib and concomitant medicines and with serious underlying medical conditions. Other reported hepatic reactions include asymptomatic increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of Bortezomib Equity (see section 4.8).

Tumour lysis syndrome

Because Bortezomib Equity is a cytotoxic medicine 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. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrhythmias and syncope. These patients should be monitored closely, and appropriate precautions taken.

Concomitant medicines

Patients should be closely monitored when given Bortezomib Equity in combination with potent CYP3A4-inhibitors. Caution should be exercised when Bortezomib Equity is combined with CYP3A4- or CYP2C19 substrates (see section 4.5).

Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics (see section 4.5).

Amyloidosis

The impact of proteasome inhibition by Bortezomib Equity on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

Potentially immunocomplex-mediated reactions

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

4.5 Interaction with other medicines 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.

An 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 % (CI 90 % [1,032 to 1,772]) based on data from 12 patients. Therefore, patients should be closely monitored when given Bortezomib Equity in combination with potent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

In an 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.

An 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. The concomitant use of Bortezomib Equity with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort.

In the same 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.

Concomitant exposure to narcotics may increase the incidence of constipation, nausea and vomiting.

An 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, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving Bortezomib Equity treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines. Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / 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

Safety in pregnancy has not been established.

If Bortezomib Equity is used during pregnancy, or if the patient becomes pregnant while receiving Bortezomib Equity, the patient needs to be informed of potential for hazards to the foetus.

Breastfeeding

Safety in lactation has not been established.

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, breastfeeding should be discontinued during treatment with Bortezomib Equity.

Fertility

Fertility studies were not conducted with Bortezomib Equity.

4.7 Effects on ability to drive and use machines

Bortezomib Equity may be associated with fatigue, dizziness, syncope and orthostatic/postural hypotension or

blurred vision. 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 4.8).

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions less frequently 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.

Frequently 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

Table 6: Adverse reactions in patients with Multiple Myeloma treated with bortezomib in clinical trials, and all post-marketing adverse reactions regardless of indication[#]

MedDRA System Organ Class	Frequency	Adverse Reaction
Infections and infestations	*Frequent*	Herpes zoster (inc. disseminated & ophthalmic), pneumonia*, herpes simplex*, fungal infection*
	Less frequent	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*, meningitis (inc. bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Less frequent*	Neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign*
Blood and lymphatic system disorders	*Frequent*	Thrombocytopenia*, neutropenia*, anaemia*, leukopenia*, lymphopenia*
	Less frequent	Pancytopenia*, febrile neutropenia, coagulopathy*, leukocytosis*, lymphadenopathy, haemolytic anaemia#, disseminated intravascular coagulation, thrombocytosis*, hyperviscosity syndrome, platelet disorder NOS, thrombotic microangiopathy (inc. thrombocytopenic purpura)#, blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration
Immune system disorders	*Less frequent*	Angioedema#, amyloidosis, hypersensitivity*, anaphylactic shock, Type III immune complex mediated reaction
Endocrine disorders	*Less frequent*	Cushing's syndrome*, hyperthyroidism*, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutrition disorders	*Frequent*	Decreased appetite, dehydration, hypokalaemia*, hyponatraemia*, blood glucose abnormal*, hypocalcaemia*, enzyme abnormality*
	Less frequent	Tumour lysis syndrome, failure to thrive*, hypomagnesaemia*, hypophosphataemia*, gout, hyperkalaemia*, abnormal uric acid*, hypercalcaemia*, hypernatraemia*, diabetes mellitus*, fluid retention, hypermagnesaemia*, electrolyte imbalance*, fluid overload, hypochloraemia*, hypovolaemia, acidosis,

		hyperchloraemia*, metabolic disorder, hyperphosphataemia*, vitamin B complex deficiency, vitamin B12 deficiency, increased appetite, alcohol intolerance
Psychiatric disorders	*Frequent*	Mood disorders and disturbances*, anxiety disorder*, sleep disorders and disturbances*
	Less frequent	Mental disorder*, hallucination*, psychotic disorder*, confusion*, restlessness, suicidal ideation*, adjustment disorder, delirium, libido decreased
Nervous system disorders	*Frequent*	Neuropathies*, peripheral sensory neuropathy, dysaesthesia*, neuralgia*, motor neuropathy*, loss of consciousness (inc. syncope), dizziness*, dysgeusia*, lethargy, headache*
	Less frequent	Tremor, peripheral sensorimotor neuropathy, dyskinesia*, cerebellar coordination and balance disturbances*, memory loss (excluding 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, 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
Eye disorders	*Frequent*	Eye swelling*, vision abnormal*, conjunctivitis*
	Less frequent	Eye haemorrhage*, eyelid infection*, chalazion#, blepharitis#, eye inflammation*, diplopia, dry eye*, eye irritation*, eye pain, increased lacrimation, eye discharge, 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	*Frequent*	Vertigo*
	Less frequent	Dysacusis (inc. tinnitus)*, hearing impaired (up to and inc. deafness), ear discomfort*, ear haemorrhage, vestibular neuronitis, ear disorder NOS
Cardiac disorders	*Less frequent*	Cardiac tamponade#, cardio-pulmonary arrest*, cardiac fibrillation (inc. atrial), cardiac failure (inc. left and right ventricular)*, dysrhythmia*, tachycardia*, palpitations, angina pectoris, pericarditis (inc. pericardial effusion)*, cardiomyopathy*, bradycardia, ventricular dysfunction*, 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	*Frequent*	Hypotension*, orthostatic hypotension, hypertension*
	Less frequent	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)*, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea*, epistaxis, upper/lower respiratory tract infection*, cough*
	Less frequent	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, 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	*Frequent*	Nausea and vomiting symptoms*, diarrhoea*,

		constipation, gastrointestinal haemorrhage (inc. mucosal)*, dyspepsia, stomatitis*, abdominal distension, oropharyngeal pain*, abdominal pain (inc. gastrointestinal and splenic pain)*, oral disorder*, flatulence
	Less frequent	Pancreatitis (inc. chronic)*, haematemesis, lip swelling*, gastrointestinal obstruction (inc. small intestinal obstruction, ileus)*, abdominal discomfort, oral ulceration*, enteritis*, gastritis*, gingival bleeding, gastro-oesophageal 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*, 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
Hepato-biliary disorders	*Frequent*	Hepatic enzyme abnormality*
	Less frequent	Hepatotoxicity (inc. liver disorder), hepatitis*, cholestasis, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis
Skin and subcutaneous tissue	*Frequent*	Rash*, pruritus*, erythema, dry skin

disorders	*Less frequent*	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*, 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	*Frequent*	Musculoskeletal pain*, muscle spasms*, pain in extremity, muscular weakness
	Less frequent	Muscle twitching, joint swelling, arthritis*, joint stiffness, myopathies*, sensation of heaviness, 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	*Frequent*	Renal impairment*
	Less frequent	Renal failure acute, renal failure chronic*, urinary tract infection*, urinary tract signs and symptoms*, haematuria*, urinary retention, micturition disorder*, proteinuria, azotaemia, oliguria*, pollakiuria, bladder irritation
Reproductive system and breast disorders	*Less frequent*	Vaginal haemorrhage, genital pain*, erectile dysfunction, testicular disorder*, prostatitis, breast

		disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders	*Less frequent*	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions	*Frequent*	Pyrexia*, fatigue, asthenia, oedema (inc. peripheral), chills, pain*, malaise*
	Less frequent	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*, 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	*Frequent*	Decreased weight
	Less frequent	Hyperbilirubinaemia*, protein analyses abnormal*, increased weight, blood test abnormal*, C-reactive protein increased, blood gases abnormal*, electrocardiogram abnormalities (inc. QT prolongation)*, international normalised ratio (INR) abnormal*, gastric pH decreased, platelet aggregation increased, troponin I increased, virus identification and serology*, urine analysis abnormal*
Injury, poisoning and	*Less frequent*	Fall, contusion, transfusion reaction, fractures*,

procedural complications		rigors*, face injury, joint injury*, burns, laceration, procedural pain, radiation injuries*
Surgical and medical procedures	*Less frequent*	Macrophage activation

NOS – Not otherwise specified

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication

Table 7: Adverse reactions in patients with Mantle Cell Lymphoma treated with VcR-CAP (i.e., bortezomib combined with rituximab, cyclophosphamide, doxorubicin, and prednisone) in a clinical trial

System Organ Class	Frequency	Adverse reaction
Infections and infestations	*Frequent*	Pneumonia*, sepsis (inc. septic shock)*, herpes zoster (inc. disseminated & ophthalmic), herpes virus infection*, bacterial infections*, upper/lower respiratory tract infection*, fungal infection*, herpes simplex*
	Less frequent	Hepatitis B, infection*, bronchopneumonia
Blood and lymphatic system disorders	*Frequent*	Thrombocytopenia*, febrile neutropenia, neutropenia*, leukopenia*, anaemia*, lymphopenia*
	Less frequent	Pancytopenia*
Immune system disorders	*Frequent*	Hypersensitivity*
	Less frequent	Anaphylactic reaction
Metabolism and nutrition disorders	*Frequent*	Decreased appetite, hypokalaemia*, blood glucose abnormal*, hyponatraemia*, diabetes mellitus*, fluid retention
	Less frequent	Tumour lysis syndrome

Psychiatric disorders	*Frequent*	Sleep disorders and disturbances*
Nervous system disorders	*Frequent*	Peripheral sensory neuropathy, dysaesthesia*, neuralgia*, neuropathies*, motor neuropathy*, loss of consciousness (inc. syncope), encephalopathy*, peripheral sensorimotor neuropathy, dizziness*, dysgeusia*, autonomic neuropathy
	Less frequent	Autonomic nervous system imbalance
Eye disorders	*Frequent*	Vision abnormal*
Ear and labyrinth disorders	*Frequent*	Dysacusis (inc. tinnitus)*
	Less frequent	Vertigo*, hearing impaired (up to and inc. deafness)
Cardiac disorders	*Frequent*	Cardiac fibrillation (inc. atrial), dysrhythmia*, cardiac failure (inc. left and right ventricular) *, myocardial ischaemia, ventricular dysfunction*
	Less frequent	Cardiovascular disorder (inc. cardiogenic shock)
Vascular disorders	*Frequent*	Hypertension*, hypotension*, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea*, cough*, hiccups
	Less frequent	Acute respiratory distress syndrome, pulmonary embolism, pneumonitis, pulmonary hypertension, pulmonary oedema (inc. acute)
Gastrointestinal disorders	*Frequent*	Nausea and vomiting symptoms*, diarrhoea*, stomatitis*, constipation, 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*
	Less frequent	Colitis (inc. clostridium difficile)*
Hepato-biliary disorders	*Frequent*	Hepatotoxicity (inc. liver disorder)
	Less frequent	Hepatic failure
Skin and subcutaneous tissue disorders	*Frequent*	Hair disorder*, pruritus*, dermatitis*, rash*
Musculoskeletal and connective tissue disorders	*Frequent*	Muscle spasms*, musculoskeletal pain*, pain in extremity
Renal and urinary disorders	*Frequent*	Urinary tract infection*
General disorders and administration site conditions	*Frequent*	Pyrexia*, fatigue, asthenia, oedema (inc. peripheral), chills, injection site reaction*, malaise*
Investigations	*Frequent*	Hyperbilirubinaemia*, protein analyses abnormal*, weight decreased; weight increased

* Grouping of more than one MedDRA preferred term.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 Equity overdose. In the event of an overdose, patients should undergo careful haemodynamic monitoring. Vital signs should be monitored, and appropriate supportive care

given to maintain blood pressure (such as fluids, pressors, and/or inotropic medicines) and body temperature (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32.

Mechanism of action

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Bortezomib mediated proteasome inhibition affects 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 tumourogenesis, 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 proapoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mL respectively after the first dose. 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 mean elimination half-life 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 following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Distribution

The mean distribution volume (V_d) of bortezomib ranged from 1 659 litres to 3 294 litres 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 100 to 1 000 mg/mL, the *in vitro* protein binding averaged 83 % 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 metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. 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. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent.

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 and18 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 51 cancer patients primarily with solid tumours 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-normalised 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 (see section 4.2, Table 5).

Renal impairment

Exposure of bortezomib is comparable in patients with various (mild, moderate to severe) degrees of renal impairment including patients receiving dialysis (see section 4.2).

The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Nitrogen

6.2 Incompatibilities

Bortezomib Equity must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

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. 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 prior to administration, with a maximum of 8 hours in the syringe.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not freeze.

For storage conditions after reconstitution of Bortezomib Equity, see section 6.3.

6.5 Nature and contents of container

Bortezomib Equity is supplied in a 10 mL/20 mm flint flat bottom tubular type-I glass vial with 20 mm dark grey bromo butyl rubber stopper (RFS) and 20 mm aluminium flip off light blue colour seals.

The vial is contained in a transparent blister pack consisting of a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

For single use only.

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

Reconstitution instructions

Bortezomib Equity 3,5 mg is for IV or SC use.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT THE HANDLING OF BORTEZOMIB EQUITY, SINCE IT CONTAINS NO PRESERVATIVE.

Bortezomib Equity is provided as a lyophilised powder in the form of a mannitol boronic ester. When reconstituted, the mannitol ester is in equilibrium with its hydrolysis product, the monomeric boronic acid.

Reconstitution for intravenous administration

Prior to use, the contents of each 10 mL vial must be reconstituted with 3,5 mL of normal (0,9 %) saline, Sodium Chloride Injection, USP.

Bortezomib Equity must not be mixed with any other medicines except for normal (0,9 %) saline, Sodium Chloride Injection, USP.

Table 8: The contents of each vial should be reconstituted only with normal (0,9 %) saline according to the following instructions based on route of administration:

	IV	**SC**
	(3,5 mg bortezomib)	**(3,5 mg bortezomib)**
Volume of diluent (0,9 % Sodium Chloride) added to reconstitute one vial	3,5 mL	1,4 mL
Final concentration after reconstitution (mg/mL)	1,0 mg/mL	2,5 mg/mL

Dissolution is completed in less than 2 minutes. 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 product must be discarded. 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. 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 prior to administration, with a maximum of 8 hours in the syringe.

Any unused product or waste material should be disposed of appropriately.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

0157

8. REGISTRATION NUMBER(S)

56/26/0040

9. DATE OF FIRST AUTHORISATION

25 April 2023