1.3.1 Summary of Product Characteristics

1. *Name of the medicinal product:*

a) Product Name: NEOMIB –2mg (Bortezomib for Injection 2mg)

***b) Strength*:** 2mg

***c) Pharmaceutical Dosage Form*:** Lyophilized Powder for Injection

2. *Qualitative and quantitative composition*

Bortezomib for Injection 2mg

Each vial contains

Bortezomib	2mg
Mannitol BP	20mg

3. Pharmaceutical form: Lyophilized Powder for Injection

4. Clinical particulars

***A.* Therapeutic indications**

Bortezomib for Injection in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

Bortezomib for Injection is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

B. Posology and method of administration

Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Posology for monotherapy

The recommended starting dose of bortezomib is 1.3mg/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.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of Bortezomib 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 therapy.

Currently there are limited data concerning re-treatment with Bortezomib.
Dose adjustments during treatment and re-initiation of treatment for monotherapy Bortezomib treatment must be withheld at the onset of any Grade 3 nonhaematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below.

Once the symptoms of the toxicity have resolved, Bortezomib treatment may be re-initiated at a 25% reduced dose (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of Bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Neuropathic pain and/or peripheral neuropathy
Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1. Patients with pre-existing severe neuropathy may be treated with Bortezomib only after careful risk/benefit assessment.

Table 1: Recommended posology modifications for Bortezomib-related neuropathy*

Severity of neuropathy	**Posology modification**
Grade 1 (Paraesthesia, weakness and/or loss of reflexes) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce Bortezomib to 1.0mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold Bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate Bortezomib treatment and reduce dose to 0.7mg/m^2 and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to	Discontinue Bortezomib

paralysis) and/or severe autonomic neuropathy	
*Based on posology modifications in Phase II and III multiple myeloma studies and post-marketing experience.	

Posology for previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplantation

Combination therapy

Bortezomib 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 is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Bortezomib is administered once weekly (days 1, 8, 22 and 29). Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each cycle.

Table 2: Recommended Posology for Bortezomib in combination with melphalan and prednisone for patients with previously untreated multiple myeloma

Twice weekly BORTEZOMIB (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 (9mg/m^2) P(60mg/m 2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once weekly BORTEZOMIB (cycles 5-9)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1.3mg/m$^{2)}$	Day 1	--	--	--	Day 8		rest period	Day 22		Day 29		rest period
M (9mg/m^2) P (60mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--		rest period	--				rest period

Vc = BORTEZOMIB; M = melphalan, P=prednisone

Dose adjustments during treatment and re-initiation of treatment for combination therapy

Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥70 x 10^9/l and the absolute neutrophils count should be ≥ 1.0 x 10^9/l
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Posology modifications during subsequent cycles in combination with melphalan and prednisone

Toxicity	**Posology modification or delay**
Haematological toxicity during a cycle	
• If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
• If platelet counts ≤30×10^9/l or	Bortezomib therapy should be withheld
ANC ≤ 0.75x10^9/l on a Bortezomib dosing day (other than Day 1)	
• If several Bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib dose should be reduced by 1 dose level (from 1.3mg/m^2 to 1 mg/m^2, or from 1mg/m^2 to 0.7mg/m^2)
Grade ≥ 3 non-haematological toxicities	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib may be reinitiated with one dose level reduction (from 1.3mg/m^2 to 1mg/m^2, or from 1mg/$m^2$to 0.7mg/m^2). For Bortezomib - related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in Table 1.

Special populations

Hepatic impairment

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first treatment 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 tolerability

Renal impairment

The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance (CrCL) > 20ml/min/1.73m^2); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20ml/min/1.73m^2). Since dialysis may reduce bortezomib concentrations, Bortezomib should be administered after the dialysis procedure.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age.

Pediatric population

The safety and efficacy of Bortezomib in children below age 18 have not yet been established.

Method of administration

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 sodium chloride 9mg/ml (0.9%) solution for injection.

C. Contraindications

- Hypersensitivity to bortezomib, boron or to any of the excipients.
- Severe hepatic impairment
- Acute diffuse infiltrative pulmonary and pericardial disease.

D. Special warnings and precautions for use

General

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). The most common haematologic toxicity is transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of Bortezomib treatment. There was no evidence of cumulative thrombocytopenia, including in the Phase II extension study. The mean platelet count nadir measured was approximately 40% of baseline. 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 ≤ 25×10^9/l during the study.

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 combination with melphalan and prednisone when the platelet count is ≤ 30,000/µl and re-initiated at a reduced dose after resolution. 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. Therefore, complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with Bortezomib.

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. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require the dose and schedule of Bortezomib to be modified. Neuropathy has been managed with supportive care and other therapies. Improvement in, or resolution of, peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral

neuropathy in the single-agent Phase III multiple myeloma study and 71% of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in Phase II studies, respectively.

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 undesirable effects are mild to moderate in nature and are observed throughout treatment. Patients developing orthostatic hypotension on Bortezomib 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, lightheadedness or fainting spells.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

RPLS, discontinue Bortezomib. The safety of reinitiating Bortezomib therapy in patients previously experiencing RPLS 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. In a single-agent Phase III randomised, comparative study the incidence of heart failure in the Bortezomib group was similar to that in the dexamethasone group.

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.

ECG 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 determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes.

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

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 (2g/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
Patients with hepatic impairment should be treated with extreme caution and a dose reduction should be considered.

Hepatic reactions
Rare cases of hepatic failure have been reported in patients receiving multiple concomitant medications 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, 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 hypoglycemic.

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.

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

An interaction study based on data from 12 patients, assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, showed a bortezomib AUC mean increase of 35% ($CI_{90\%}$ [1.032 to 1.772]). Therefore patients should be closely monitored when given

bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In an interaction study based on data from 17 patients, assessing the effect of omeprazole, a potent CYP2C19 inhibitor, there was no significant effect on the pharmacokinetics of bortezomib.
In the absence of interaction studies investigating the effect of CYP3A4 inducers on the pharmacokinetics of bortezomib, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inducers (e.g. rifampicin).

An interaction study assessing the effect of melphalan-prednisone on bortezomib showed a 17% increase in mean bortezomib AUC 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 Bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics

F. Pregnancy and lactation 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 parturition and post-natal development were not conducted Bortezomib should not be used during pregnancy unless the clinical condition of the woman requires treatment with Bortezomib.

Contraception in males and females

For Bortezomib no clinical data with regard to exposure during pregnancy are available. Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.

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

Breastfeeding

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious undesirable effects in breast-fed

infants, lactation should be discontinued during treatment with Bortezomib.

Fertility

Fertility studies were not conducted with Bortezomib.

G. Effects on ability to drive and use machines

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

H. Undesirable effects

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

The following undesirable effects in Table 4 were considered by the investigators to have at least a possible or probable causal relationship to Bortezomib during the conduct of 5 non-comparative Phase II studies and 1 comparative Phase III trial (Bortezomib vs dexamethasone) in 663 patients with relapsed or refractory multiple myeloma, of whom 331 received Bortezomib as single agent. The safety

database comprises data from patients with multiple myeloma or B-cell lymphocytic leukemia (CLL). In addition, this table contains adverse reactions from postmarketing reports* with frequency categorization estimated from safety data comprising 2017 patients from clinical trials (including the patients from the 6 studies described above). These patients were from company-sponsored trials with Bortezomib studied at 1.3 mg/m^2 as single chemotherapeutic agent or in combination with dexamethasone for multiple myeloma (1995 patients), or for B cell chronic lymphocytic leukemia (22 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 4: Adverse reactions in patients with relapsed/refractory multiple myeloma

Infections and infestations *Very common*: herpes zoster (including disseminated). *Common*: pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex. *Uncommon*: septic shock*, sepsis, herpes meningoencephalitis*, bacteraemia, pneumonia pneumococcal, bronchopneumonia, upper and lower respiratory tract infection, catheter related infection, pleural infection, haemophilus infection, cytomegalovirus infection, influenza, infectious mononucleosis, varicella, urinary tract infection, gastroenteritis, candidal infection, fungal infection, post herpetic neuralgia, oral candidiasis, blepharitis, infection.
Neoplasms benign and malignant (including cysts and polyps) *Uncommon*: tumour lysis syndrome
Blood and lymphatic system disorders *Very common*: thrombocytopenia, neutropenia, anaemia**.** *Common***:** leukopenia, lymphopenia**.** *Uncommon***:** pancytopenia, febrile neutropenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy.
Immune system disorders *Uncommon*: angioedema*, hypersensitivity, immunocomplex mediated hypersensitivity, potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis

Endocrine disorders *Uncommon***:** inappropriate antidiuretic hormone (ADH) secretion**.**
Metabolism and nutrition disorders *Very common*: appetite decreased. *Common***:** dehydration, hypokalaemia, hyperglycaemia. Uncommon**:** hyperkalaemia, cachexia, hypercalcaemia, hypocalcaemia, hypernatraemia, hyponatraemia, hypoglycaemia, hyperuricaemia, vitamin B12 deficiency, appetite increased, hypomagnesaemia, hypophosphataemia.
Psychiatric disorders *Common*: confusion, depression, insomnia, anxiety. *Uncommon*: agitation, delirium, hallucinations, restlessness, mood swings, mental status changes, sleep disorder, irritability, abnormal dreams.

Nervous system disorders *Very commo*n: peripheral neuropathy, peripheral sensory neuropathy, paraesthesia, headache. *Common*: polyneuropathy, peripheral neuropathy aggravated, dizziness (excluding vertigo), dysgeusia, dysaesthesia, hypoaesthesia, tremor. *Uncommon*: encephalopathy*, reversible posterior leukoencephalopathy syndrome* paraplegia, intracranial haemorrhage, subarachnoid haemorrhage convulsions peripheral motor neuropathy, syncope, paresis, disturbance in attention, increased activity, ageusia, somnolence, migraine, cognitive disorder, jerky movements, dizziness postural, sciatica, mononeuropathy, speech disorder, restless leg syndrome. *Rare*: autonomic neuropathy*
Eye disorders *Common:* vision blurred eye pain. *Uncommon:* eye haemorrhage, vision abnormal, dry eye, conjunctivitis, eye discharge, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling. *Rare*: herpes zoster ophthalmic*
Ear and labyrinth disorders *Common*: vertigo. *Uncommon*: deafness, tinnitus, hypoacusis, hearing impaired**.**

Cardiac disorders *Uncommon*: cardiac tamponade*, cardiopulmonary arrest*, cardiac arrest, cardiogenic shock, myocardial infarction, angina pectoris, angina unstable, development or exacerbation of congestive heart failure cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, atrioventricular block complete, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations. *Rare*: new onset of decreased left ventricular ejection fraction, pericarditis*, ventricular arrhythmia*, ventricular tachycardia*
Vascular disorders *Common*: hypotension, orthostatic and postural hypotension, phlebitis, haematoma, hypertension. *Uncommon*: cerebral hemorrhage, vasculitis, cerebrovascular accident, pulmonary hypertension, petechiae, ecchymosis, purpura, vein discolouration, vein distended, wound hemorrhage, flushing, hot flushes**.**
Respiratory, thoracic and mediastinal disorders *Very Common*: dyspnoea. *Common*: dyspnoea exertional, epistaxis, cough, rhinorrhoea. *Uncommon*: respiratory failure*, pneumonitis*, pulmonary embolism*, pulmonary hypertension*, interstitial pneumonia*, acute diffuse infiltrative pulmonary disease*, pulmonary alveolar haemorrhage*, respiratory arrest, hypoxia, pulmonary congestion, pleural effusion, asthma, respiratory alkalosis, tachypnoea, wheezing, nasal congestion,hoarseness, rhinitis, hyperventilation, orthopnoea, chest wall pain, sinus pain, throat tightness, productive cough. *Rare*: acute respiratory distress syndrome (ARDS)*, peripheral embolism*
Gastrointestinal disorders *Very common:* vomiting, diarrhoea, nausea, constipation. *Common*: abdominal pain, stomatitis, dyspepsia, loose stools, abdominal pain upper, flatulence, abdominal distension, hiccups, mouth ulceration, pharyngolaryngeal pain,

dry mouth. *Uncommon*: colitis ischaemic*, acute pancreatitis, ileus paralytic, antibiotic associated colitis, colitis, haematemesis, diarrhoea haemorrhagic, gastrointestinal haemorrhage, rectal haemorrhage, enteritis, dysphagia, abdominal discomfort, eructation, gastrointestinal motility disorder, oral pain, retching, change in bowel habit, spleen pain, oesophagitis, gastritis, gastro-oesophageal reflux disease, gastrointestinal pain, gingival bleeding, gingival pain, hiatus hernia, irritable bowel syndrome, oral mucosal petechiae, salivary hypersecretion, tongue coated, tongue discolouration, faecal impaction.

Hepato-biliary disorders *Uncommon:* hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia**.** *Rare*: hepatic failure*
Skin and subcutaneous tissue disorders *Very commo*n: rash. *Common*: periorbital oedema, urticaria, rash pruritic, pruritus, erythema, sweating increased, dry skin, eczema. *Uncommon:* Stevens-Johnson Syndrome*, toxic epidermal necrolysis*, rash erythematous, photosensitivity reaction, contusion, pruritus generalised, rash macular, rash papular, psoriasis, rash generalized, eyelid oedema, face oedema, dermatitis, alopecia, nail disorder, skin discolouration, dermatitis atopic, hair texture abnormal, heat rash, night sweats, pressure sore, ichthyosis, skin nodule. *Rare*: acute febrile neutrophilic dermatosis (Sweet's syndrome)*, vasculitic rash (including leukocytoclastic vasculitis)*
Musculoskeletal, connective tissue and bone disorders *Very Common:* myalgia. *Common*: muscle weakness, musculoskeletal pain, pain in limb, muscle cramps, arthralgia, bone pain, back pain, peripheral swelling. *Uncommon*: muscle spasms, muscle twitching or sensation of heaviness, muscle stiffness, joint swelling, joint stiffness, buttock pain, swelling, pain in jaw.
Renal and urinary disorders *Common*: renal impairment, dysuria. *Uncommon*: renal failure acute, renal failure, oliguria, renal colic, haematuria, proteinuria, urinary retention, urinary frequency, difficulty in micturition, loin pain, urinary incontinence, micturition urgency.
Reproductive system and breast disorders *Uncommon*: testicular pain, erectile dysfunction.
General disorders and administration site conditions *Very Commo*n: fatigue pyrexia. *Common*: asthenia, weakness, lethargy, rigors, malaise, influenza like illness, oedema peripheral, chest pain, pain, oedema. *Uncommon*: fall, mucosal haemorrhage, mucosal inflammation, neuralgia, injection site phlebitis, extravasation inflammation tenderness, injection site erythema, feeling cold, chest pressure sensation, chest discomfort, groin pain, chest tightness.
Investigations *Common*: weight decreased, blood lactate dehydrogenase increased. *Uncommon*: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood alkaline phosphatase increased, blood creatinine increased, blood urea increased, gamma-glutamyltransferase increased, blood amylase increased, liver function tests abnormal, red blood cell count decreased, white blood cell

count decreased, blood bicarbonate decreased, heart rate irregular, C-reactive protein
increased, blood phosphate decreased, weight increased.
Injury and poisoning *Uncommon*: catheter related complications, post procedural pain, post procedural haemorrhage, burns.

*from postmarketing sources

Summary of safety data in patients with previously untreated multiple myeloma:

The following table 5 describes safety data from 340 patients with previously untreated multiple myeloma who received Bortezomib (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective Phase III study.

Overall, the safety profile of patients treated with Bortezomib in monotherapy was similar to that observed in patients treated with Bortezomib in combination with melphalan and prednisone.

Table 5: Treatment emergent drug-related adverse reactions reported in ≥ 10% of patients treated with Bortezomib in combination with melphalan and prednisone

	Vc+M+P			***M+P***		
	(n=340)			*(n=337)*		
MedDRA System Organ Class	*Total*	*Toxicity Grade, n (%)*		*Total*	*Toxicity Grade, n (%)*	
Preferred Term	*n (%)*	*3*	*≥ 4*	*n (%)*	*3*	*≥ 4*
Infections and Infestations						
Herpes Zoster	*39 (11)*	*11 (3)*	*0*	*9 (3)*	*4 (1)*	*0*
Blood and lymphatic system disorders						
Thrombocytopenia	*164 (48)*	*60 (18)*	*57 (17)*	*140 (42)*	*48 (14)*	*39 (12)*
Neutropenia	*160 (47)*	*101 (30)*	*33 (10)*	*143 (42)*	*77 (23)*	*42 (12)*

Anaemia	*109 (32)*	*41 (12)*	*4 (1)*	*156 (46)*	*61 (18)*	*18 (5)*
Leukopenia	*108 (32)*	*64 (19)*	*8 (2)*	*93 (28)*	*53 (16)*	*11 (3)*
Lymphopenia	*78 (23)*	*46 (14)*	*17 (5)*	*51 (15)*	*26 (8)*	*7 (2)*
Metabolism and nutrition disorders						
Anorexia	*64 (19)*	*6 (2)*	*0*	*19 (6)*	*0*	*0*
Psychiatric disorders						
Insomnia	*35 (10)*	*1 (<1)*	*0*	*21 (6)*	*0*	*0*
Nervous system disorders						
Peripheral Neuropathy	*156 (46)*	*42 (12)*	*2 (1)*	*4 (1)*	*0*	*0*
Neuralgia	*117*	*27*	*2 (1)*	*1 (<1)*	*0*	*0*
	(34)	*(8)*				
Paraesthesia	*42 (12)*	*6 (2)*	*0*	*4 (1)*	*0*	*0*
Gastrointestinal disorders						
Nausea	*134 (39)*	*10 (3)*	*0*	*70 (21)*	*1 (<1)*	*0*
Diarrhoea	*119 (35)*	*19 (6)*	*2 (1)*	*20 (6)*	*1 (<1)*	*0*
Vomiting	*87 (26)*	*13 (4)*	*0*	*41 (12)*	*2 (1)*	*0*
Constipation	*77 (23)*	*2 (1)*	*0*	*14 (4)*	*0*	*0*
Abdominal Pain Upper	*34 (10)*	*1 (<1)*	*0*	*20 (6)*	*0*	*0*
Skin and subcutaneous tissue disorders						
Rash	*38 (11)*	*2 (1)*	*0*	*7 (2)*	*0*	*0*
General disorders and administration site conditions						
Fatigue	*85 (25)*	*19 (6)*	*2 (1)*	*48 (14)*	*4 (1)*	*0*

Asthenia	*54 (16)*	*18 (5)*	*0*	*23 (7)*	*3 (1)*	*0*
Pyrexia	*53 (16)*	*4 (1)*	*0*	*19 (6)*	*1 (<1)*	*1 (<1)*

Herpes zoster virus reactivation
Antiviral prophylaxis should be considered in patients being treated with Bortezomib. 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 Vc+M+P compared with M+P (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

I. Overdose

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

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

5. Pharmacological properties

A. Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agent
ATC code: L01XX32

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 proapoptotic 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.

Clinical efficacy in previously untreated multiple myeloma
A prospective Phase III, international, randomized (1:1), open-label clinical study (VISTA) of 682 patients was conducted to determine whether BORTEZOMIB (1.3mg/m^2) in combination with melphalan (9mg/m^2) and prednisone (60mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9mg/m^2) and prednisone (60mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in Table 6.

Table 6: Summary of baseline patient and disease characteristics in the VISTA study

Patient Characteristics	**Vc+M+P n=344**	**M+P n=338**
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51%/49%	49%/51%
Race: Caucasian/asian/black/other	88%/10%/1%/1%	87%/11%/2%/0%
Karnofsky performance status score ≤ 70	35%	33%
Hemoglobin <100 g/l	37%	36%
Platelet count <75 x 10^9/l	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64%/24%/8%	62%/26%/8%
Median β_2-microglobulin (mg/l)	4.2	4.3
Median albumin (g/l)	33.0	33.0
Creatinine clearance ≤ 30 ml/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the M+P arm were offered Vc+M+P treatment. Median follow-up was 16.3 months. A survival update was performed with a median duration of follow-up of 36.7 months. A statistically significant survival benefit in favour of the Vc+M+P treatment group was observed (HR=0.65; p=0.00084) despite subsequent therapies including Bortezomib-based regimens. While the median survival in M+P treatment group has now been estimated at 43.1 months, the median survival on the Vc+M+P treatment group has not been reached. Efficacy results are presented in Table 7:

Table 7: Updated efficacy results following pre-planned interim analysis in the VISTA study

Efficacy endpoint	**Vc+M+P n=344**	**M+P n=338**
Time to progression		
Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)

Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value [c]	0.000002	
Progression-free survival Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall survival* Events (deaths) n (%)	109(32)	148 (44)
Median[a] (95% CI)	NR (46.2, NR)	43.1 mo (34.8, NR)
Hazard ratio[b] (95% CI)	0.65 (0.51, 0.84)	
p-value [c]	0.00084	
Response rate population[e] n = 668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in serum M-protein population[g] n=667	n=336	n=331
>=90% n (%)	151 (45)	34 (10)
Time to first response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] response duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to next therapy Events n (%)	73 (21)	127 (38)
Median[a] (95% CI)	NE (26.1, NE)	20.8 mo (18.3, 28.5)
Hazard ratio[b] (95% CI)	0.52 (0.39, 0.70)	

p-value [c]	0.000009

[a] Kaplan-Meier estimate. [b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP

[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region

[d] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chisquare test adjusted for the stratification factors

[e] Response population includes patients who had measurable disease at baseline [f] EBMT criteria

[g] All randomized patients with secretory disease

* Survival update based on a median duration of follow-up at 36.7 months

NE: not estimable

NR: not reached

mo: months

Clinical efficacy in relapsed or refractory multiple myeloma

The safety and efficacy of BORTEZOMIB were evaluated in 2 studies at the recommended dose of 1.3mg/m^2: a Phase III randomized, comparative study, versus dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a Phase II single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment.

Table 8: Dosing regimens in Phase II and Phase III studies

Phase/arm	**Treatment schedule**	**Dose**	**Regimen**
II	Vc: Day 1,4,8,11, (rest Day 12-21)	1.3mg/m^2 (intravenous bolus)	Q3 weeks x8 cycles (extension**)
III	Vc* a) Days 1,4,8,11, (Rest Day 12 – 21) b) Days 1,8,15,22	1.3mg/m^2 (intravenous bolus)	a) Q3weeks x 8, then b) Q5 weeks x 3
III	Dex a) Days 1–4, 9–12, 17–20	40 mg (oral)	a) Q5 week x 4 b) Q4 week x 5

	b) Days 1–4		
II	Add Dex***	20 mg (oral) (Days 1,2,4,5,8,9, 11,12)	Q3 weeks

*a) is the initial treatment, a) and b) represent a full course of treatment
**An extension study authorised patients benefiting from treatment to continue receiving BORTEZOMIB
***If after 2 or 4 cycles of BORTEZOMIB, the patients had progressive disease or stable disease, respectively, they could receive dexamethasone

Table 9: Patient characteristics in Phase II and Phase III studies

	Phase II Vc	**Phase III Vc**	**Phase III Dex**
Patient number, ITT analysis	202	333	336
Male %	60	56	60
Median age, yrs (range)	59 (34-84)	61 (33-84)	61 (27-86)
Caucasian	81%	90%	88%
Karnofsky PS>80%	80%	87%	84%
Platelets < 75,000/µl	21%	6%	4%
Hemoglobin < 100g/l	44%	32%	28%
Median Creatinine Clearance, ml/min (range)	74 (14-221)	73.3 (15.6-170.7)	73.3 (15.3-261.1)
Myeloma IgG	60%	60%	59%
Myeloma IgA	24%	23%	24%
Myeloma light chain	14%	12%	13%
Median duration since diagnosis (yrs)	4.0	3.5	3.1
Chromosome 13 abnormalities	15%	25.7%	25.0%
Median β_2 microglobulin (mg/l)	3.5	3.7	3.6
Median number prior treatment lines* (range)	6 (2-15)	2 (1-7)	2 (1-8)
1 prior line > 1 prior line	0	n =132 (40%) n = 186 (60%)	n = 119 (35%) n = 194 (65%)

*Including steroids, alkylating agents, anthracyclines, thalidomide and stem cell transplants

Table 10: Patient exposure to treatment with BORTEZOMIB during Phase II and III studies

	Phase II Vc	**Phase III Vc**	**Phase III Dex**
Received at least 1 dose	n = 202	n =331	n = 332
Completed 4 cycles a) all initial cycles (number) b) full course (number) c) extension *	62% 27% (8 cycles) NA n = 63 pts (median 7 cycles) or total median 14 cycles (range 7-32)	69% 29% (8 cycles) 9% (11 cycles) NA	36% (4 cycles) 5% (9 cycles) NA

*Patients could continue on treatment after completing 8 cycles, in case of benefit NA = not applicable

In the Phase III study, treatment with Bortezomib led to a significantly longer time to progression, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone (see Table 11), in all patients as well as in patients who have received 1 prior line of therapy. As a result of a preplanned interim analysis, the dexamethasone arm was halted at the recommendation of the data monitoring committee and all patients randomised to dexamethasone were then offered Bortezomib, regardless of disease status. Due to this early crossover, the median duration of follow-up for surviving patients is 8.3 months. Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the Bortezomib arm.

Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for Bortezomib independently of age. Regardless of β_2- microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the Bortezomib arm.

In the refractory population of the Phase II study, responses were determined by an independent review committee and the response criteria were those of the European Bone Marrow Transplant Group. The median survival of all patients enrolled was 17 months (range <1 to 36+ months). This survival was greater than the six-to-nine

month median survival anticipated by consultant clinical investigators for a similar patient population. By multivariate analysis, the response rate was independent of myeloma type, performance status, chromosome 13 deletion status, or the number or type of previous therapies. Patients who had received 2 to 3 prior therapeutic regimens had a response rate of 32% (10/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67)

Table 11: Summary of Disease Outcomes from the Phase III and Phase II studies

	Phase III		**Phase III**		**Phase III**		**Phase II**
	All patients		**1 line of Prior therapy**		**>1 Prior line of therapy**		**≥ 2 prior lines**
Time related events	**Vc n =333[a]**	**Dex n =336[a]**	**Vc n =132[a]**	**Dex n =119[a]**	**Vc n =200[a]**	**Dex n =217[a]**	**Vc n =202[a]**
TTP, days [95% CI]	189[b] [148, 211]	106[b] [86, 128]	212[d] [188, 267]	169[d] [105, 191]	148[b] [129, 192]	87[b] [84, 107]	210 [154, 281]
1 year survival, % [95% CI]	80[d] [74,85]	66[d] [59,72]	89[d] [82,95]	72[d] [62,83]	73 [64,82]	62 [53,71]	60
Best response (%)	**Vc n =315[c]**	**Dex n =312[c]**	**Vc n =128**	**Dex n =110**	**Vc n =187**	**Dex n =202**	**Vc n=193**
CR	20 (6) [b]	2 (<1) [b]	8 (6)	2 (2)	12 (6)	0 (0)	(4)**
CR + nCR	41 (13) [b]	5 (2) [b]	16 (13)	4 (4)	25 (13)	1 (<1)	(10)**
CR+ nCR + PR	121 (38) [b]	56 (18) [b]	57 (45) [d]	29 (26) [d]	64 (34) [b]	27 (13) [b]	(27)**
CR + nCR+ PR+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	63 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	126 (4.1)	385*

Time to response CR + PR (days)	43	43	44	46	41	27	38*

[a] Intent to Treat (ITT) population [b] p-value from the stratified log-rank test; analysis by line of therapy excludes stratification for therapeutic history; p<0.0001 [c] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.
[d] p-value from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors; analysis by line of therapy excludes stratification for therapeutic history
*CR+PR+MR **CR=CR, (IF-); nCR=CR (IF+)
NA = not applicable, NE = not estimated

In the Phase II study, patients who did not obtain an optimal response to therapy with Bortezomib alone were able to receive high-dose dexamethasone in conjunction with Bortezomib (see Table 8). The protocol allowed patients to receive dexamethasone if they had had a less than optimal response to Bortezomib alone.

A total of 74 evaluable patients were administered dexamethasone in combination with Bortezomib. Eighteen percent of patients achieved, or had an improved response (MR (11%) or PR (7%)) with combination treatment.

Patients with previously treated light-chain (AL) Amyloidosis
An open label non randomised phase 1/2 study was conducted to determine the safety and efficacy of Bortezomib in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular Bortezomib did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis, a 67.3% response rate (including a 28.6% CR rate) as measured by hematologic response (M‑protein) was reported in 49 evaluable patients treated with the maximum allowed doses of 1.6 mg/m^2 weekly and 1.3 mg/m^2 twice-weekly. For these dose cohorts, the combined 1‑year survival rate was 88.1%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Bortezomib in all subsets of the paediatric population in multiple myeloma. This medicinal product has been authorised under “Exceptional Circumstances”. This means that for

scientific reasons it has not been possible to obtain complete information on this medicinal product.

B. Pharmacokinetic properties

Following intravenous bolus administration of a 1.0mg/m^2 and 1.3mg/m^2 dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50ml/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106ng/ml for the 1.0mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose.

Distribution

The mean distribution volume (V_d) of bortezomib ranged from 1659 l to 3294 l following single- or repeated – dose administration of 1.0mg/m^2 or 1.3mg/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 1.0µg/ml, the *in vitro* protein binding averaged 82.9% in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration – dependent.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P_{450} isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P_{450} enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronatedbortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination

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 1.0mg/m^2 and 1.3mg/m^2, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0mg/m^2 and 1.3mg/m^2, respectively.

C. Preclinical safety data

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells (CHO) at concentrations as

low as 3.125µg/ml, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.
Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic dosages, but no direct embryo-foetal toxicity below maternally toxic dosages. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6 –month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea, haematopoietic and lymphatic tissues resulting in peripheral blood cytopenias, lymphoid tissue atrophy and hematopoietic bone marrow hypocellularity: peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment. Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

6. *Pharmaceutical particulars*

A. List of excipients

Mannitol BP
Water for Injection USP

B. Incompatibilities

This medicinal product must not be mixed with other medicinal products.

C. Shelf life: 2 Years

D. Special precautions for storage

Store at controlled room temperature 25°C (77°F). Protect from light.

E. Nature and contents of container: 15ml

glass vial Pack containing 1 single-use vial.

F. Special precautions for disposal

General precautions

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

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

Instructions for reconstitution

Reconstituted solution:

Each vial of NEOMIB 2 mg must be reconstituted with 2 mL of (0.9%) sodium chloride injection USP.

Reconstitute solution should be clear and colorless solution.

Product should be inspected for particulate matter and discoloration prior to administration. If any particulate matter or discoloration has been observed during any point of time, the reconstituted product should not be used.

When reconstituted as directed, Bortezomib may be stored at 25°C (77°F). Reconstituted Bortezomib should be administered within 8 hours of preparation, the reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for upto 8 hours in a syringe; however total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

Disposal

For single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

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