JANSSEN-CILAG Ltd

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IMPORTANT SAFETY INFORMATION

Contraindication of Velcade (Bortezomib) in patients with acute diffuse infiltrative pulmonary and pericardial disease

Dear Healthcare Professional,

Summary

Janssen-Cilag International NV would like to inform you that the European Medicines Agency (EMEA) has recommended that Velcade (bortezomib) should not be used in multiple myeloma patients who are diagnosed with acute diffuse infiltrative pulmonary and pericardial disease .

As part of the continuous monitoring of medicines the EMEA reviewed all currently available information on the safety of Velcade. The EMEA's Committee for Medicinal Products for Human Use (CHMP) concluded during its March 2008 meeting that the benefits of Velcade are greater than its risks, except in patients with acute diffuse infiltrative pulmonary and pericardial disease. The CHMP therefore recommended contraindicating the use of Velcade for these patients.

The information in this 'Dear Healthcare Professional Communication' has been endorsed by the European Medicines Agency's scientific committee, the Committee for Medicinal Products for Human Use (CHMP).

Further information on the safety concern

Velcade is indicated as mono-therapy 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.

Based on the reviewed data and the observed pulmonary drug-induced disease, the CHMP considers that a contraindication in patients with *acute diffuse infiltrative pulmonary disease* represents the best way to prevent adverse and fatal events due to pulmonary toxicity. In addition, based on the review of cardiac disorders and serious adverse events associated with fluid retention, the CHMP considers that Velcade should also be contraindicated in patients with *pericardial disease.*

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In addition, the CHMP recommended strengthening the existing warnings on pulmonary disorders by advising to perform baseline chest X-rays to determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes. You are also advised to consider individual benefit-risk profiles, before starting patients on treatment with Velcade. Finally, the CHMP also recommended that new information on cardiac and pulmonary undesirable effects observed during the post-marketing phase be included in the product information.

We remind prescribers that the full contraindications for Velcade are now as follows:
"Hypersensitivity to bortezomib, boron or to any of the excipients.
Severe hepatic impairment.
Acute diffuse infiltrative pulmonary and pericardial disease."

Call for reporting

We remind you that any suspected adverse reactions should be reported to the local representative of the Marketing Authorisation Holder or to the Irish Medicines Board, in the usual way,

Communication information

Should you require any further information then please contact Medical Information, Janssen-Cilag Ltd, on 1800 709122.

Yours faithfully

PMF Barnes MBBS FFPM
Medical Director, Janssen-Cilag Ltd

Annexe:
Text of the revised Product Information (with changes made visible)

1. NAME OF THE MEDICINAL PRODUCT

VELCADE 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 injection contains 1 mg bortezomib.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VELCADE is indicated as mono-therapy 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.

4.2 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.

Recommended dosage

The recommended starting dose of bortezomib 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 VELCADE.

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

Currently there are limited data concerning retreatment with VELCADE.

Recommended dosage adjustments during treatment and re-initiation of treatment

VELCADE 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 also section 4.4). Once the symptoms of the toxicity have resolved, VELCADE 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 VELCADE must be considered unless the benefit of treatment clearly outweighs the risk.

Patients who experience VELCADE 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 VELCADE only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for VELCADE related neuropathy.

Severity of neuropathy	**Modification of dose and regimen (see section 4.4)**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELCADE treatment and reduce dose to 0.7 mg/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 paralysis) And/or severe autonomic neuropathy	Discontinue VELCADE

*Based on dose modifications in phase II & III multiple myeloma studies and post-marketing experience.

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

Paediatric patients

The experience in children and adolescents is limited. Therefore, it should not be used in the paediatric age group until further data become available.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (see section 4.8).

Use in patients with impaired renal function

VELCADE has not been formally studied in patients with impaired renal function. Patients with compromised renal function should be monitored carefully, especially if creatinine clearance is ≤30 ml/min and a dose reduction should be considered (see section 4.4 and 4.8).

Use in patients with impaired hepatic function

VELCADE has not been studied in patients with impaired hepatic function. Significant hepatic impairment may have an impact on the elimination of bortezomib and may increase the likelihood of drug-drug interactions. Patients with impaired liver function should be treated with extreme caution and a dose reduction should be considered (see sections 4.3 and 4.4).

4.3 Contraindications

Hypersensitivity to bortezomib, boron or to any of the excipients.

Severe hepatic impairment.

Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

Gastrointestinal

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with VELCADE treatment. Cases of ileus have been reported, therefore patients who experience constipation should be closely monitored.

Haematological

VELCADE 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 VELCADE 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 $\leq 25 \times 10^9$/l during the study. Platelet counts should be monitored prior to each dose of VELCADE. Therapy should be held when the platelet count is <25,000/µl and re-initiated at a reduced dose after resolution (see section 4.2). 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 VELCADE.

Peripheral Neuropathy

Treatment with VELCADE 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 VELCADE to be modified (see section 4.2). 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 phase III 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

VELCADE 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 VELCADE did not have evidence of orthostatic hypotension prior to treatment with VELCADE. 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 VELCADE. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

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 phase III randomized, comparative study the incidence of heart failure in the VELCADE 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 VELCADE (see section 4.8). Some of these events have been fatal. ~~A higher proportion of these events has been reported in Japan.~~ A pretreatment 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 VELCADE therapy.

In a clinical trial, two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. 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

The incidence of serious undesirable effects has been shown to increase in patients with mild to moderate renal impairment compared to patients with normal renal function (see section 4.8). Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely and dose reduction considered.

Hepatic Impairment

Patients with hepatic impairment should be treated with extreme caution and a dose reduction should be considered (see sections 4.2 and 4.3).

Hepatic Reactions

Rare cases of acute liver 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 (see section 4.8).

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.

Amyloidosis

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

Precautions with certain concomitant medicinal products

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

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

Potentially immunocomplex-mediated reactions

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

4.5 Interaction with other medicinal products and other forms of interaction

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

A drug-drug 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 a drug-drug 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.

Patients should be closely monitored when given bortezomib in combination with CYP2C19-inhibitors (e.g. fluoxetine).

In the absence of drug-drug interaction studies investigating the effect of CYP3A4-inducers on the PK of bortezomib, patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inducers (e.g. rifampicin).

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

4.6 Pregnancy and lactation

For VELCADE no clinical data on exposed pregnancies are available. 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 dosages. Animal studies were not conducted to determine the parturition and post-natal development (see section 5.3)

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 3 months following VELCADE therapy. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient needs to be informed of potential for hazards to the foetus.

It is not known whether VELCADE is excreted in human milk. Because of the potential for serious undesirable effects in breast-fed infants from VELCADE, women are advised against breast feeding while receiving VELCADE.

4.7 Effects on ability to drive and use machines

VELCADE may have a moderate influence on the ability to drive and use machines. VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when operating machinery, or when driving (see section 4.8).

4.8 Undesirable effects

The following undesirable effects were considered to have at least a possible or probable causal relationship to VELCADE by the investigators during the conduct of 5 non-comparative Phase II studies and 1 comparative phase III trial VELCADE vs dexamethasone in 663 patients with relapsed or refractory multiple myeloma, of whom 331 received VELCADE as single agent. The safety database comprises data from patients with multiple myeloma or B-cell lymphocytic leukemia (CLL). Patients were treated with VELCADE as a single agent, or in combination with dexamethasone.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very common: herpes zoster (including disseminated).
Common: pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex.
Uncommon: sepsis, 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, malignant and unspecified (including cysts and polyps) Uncommon: tumour lysis syndrome (see section 4.4).
Blood and lymphatic system disorders (see section 4.4) Very Common: thrombocytopenia, neutropenia, anaemia. Common: leukopenia, lymphopenia. Uncommon: pancytopenia, febrile neutropenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy.
Immune system disorders Uncommon: hypersensitivity, immunocomplex mediated hypersensitivity, potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis (see section 4.4).
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(see sections 4.4 and 4.7) Very Common: peripheral neuropathy, peripheral sensory neuropathy (see section 4.4), paraesthesia, headache. Common: polyneuropathy, peripheral neuropathy aggravated, dizziness (excluding vertigo), dysgeusia, dysaesthesia, hypoaesthesia, tremor. Uncommon: paraplegia, intracranial haemorrhage, subarachnoid haemorrhage convulsions (see section 4.4), 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.
Eye disorders Common: vision blurred (see section 4.7), eye pain. Uncommon: eye haemorrhage, vision abnormal, dry eye, conjunctivitis, eye discharge, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.
Ear and labyrinth disorders Common: vertigo. Uncommon: deafness, tinnitus, hypoacusis, hearing impaired.
Cardiac disorders Uncommon: cardiac arrest, cardiogenic shock, myocardial infarction, angina pectoris, angina unstable, development or exacerbation of congestive heart failure (see section 4.4), 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.
Vascular disorders Common: hypotension, orthostatic and postural hypotension (see sections 4.4 and 4.7), 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 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.
Gastrointestinal disorders (see section 4.4) 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: 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.
Hepatobiliary disorders (see section 4.4) Uncommon: hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia.
Skin and subcutaneous tissue disorders Very Common: rash. Common: periorbital oedema, urticaria, rash pruritic, pruritus, erythema, sweating increased, dry skin, eczema. Uncommon: vasculitic rash, 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.
Musculoskeletal and connective tissue 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 Common: fatigue (see section 4.7), 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, poisoning and procedural complications Uncommon: catheter related complications, post procedural pain, post procedural haemorrhage, burns.

Post Marketing Experience

Clinically significant adverse reactions are listed if they have been reported during post approval use of VELCADE and may or may not have been reported in clinical trials. Their frequency is not known.

Infections and infestations

Herpes meningoencephalitis

Immune System Disorders

Angioedema

Nervous system disorders

Encephalopathy, autonomic neuropathy

Eye disorders

Ophthalmic herpes

Cardiac disorders

Cardiac tamponade, pericarditis, cardiac and cardiopulmonary arrest, ventricular arrhythmias, atrio-ventricular block complete, atrial fibrillation, tachycardia, sinus and ventricular tachycardia

Respiratory, thoracic and mediastinal disorders (see section 4.4)

Pneumonitis, pneumonia, interstitial pneumonia, Acute Respiratory Distress Syndrome (ARDS), acute diffuse infiltrative pulmonary disease, pulmonary hypertension, respiratory failure, pulmonary alveolar haemorrhage, acute pulmonary oedema, pulmonary oedema, pulmonary embolism, peripheral embolism

Gastrointestinal disorders

Ischemic colitis

Hepatobiliary disorders

Liver failure

4.9 Overdose

In patients, overdosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes (Refer to section 5.3 for preclinical cardiovascular safety pharmacology studies).

There is no known specific antidote for VELCADE overdosage. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent
ATC code: LO1XX32

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. The European Medicines Agency (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 orchestrating 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 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.

Clinical Trials

The safety and efficacy of VELCADE were evaluated in 2 studies at the recommended dose of 1.3 mg/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. (See Tables 2 3 and 4).

Table 2: Dosing regimens in Phase II and Phase III studies

Phase/arm	Drug Schedule	Dose	Regimen
II	VELCADE: Day 1,4,8,11, (rest Day 12-21)	1.3 mg/m^2 (IV bolus)	Q3 weeks x 8cycles (extension**)
III	VELCADE* a) Days 1,4,8,11, (Rest Day 12-21) b) Days 1,8,15,22	1.3 mg/m^2 (IV bolus)	a) Q3weeks x 8, then b) Q5 weeks x 3
III	DEXAMETHASONE ~~c)~~a) **Days 1–4, 9–12, 17–20**~~b)~~ **Days 1–4**	40 mg (PO)	a) Q5 week x 4 b) Q4 week x 5

Phase/arm	Drug Schedule	Dose	Regimen
II	Add DEXAMETHASONE***	20 mg (PO) (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 VELCADE
***If after 2 or 4 cycles of VELCADE, the patients had progressive disease or stable disease, respectively, they could receive dexamethasone

Table 3: Patient characteristics in Phase II and Phase III studies

	Phase II VELCADE	Phase III VELCADE	Phase III Dex
Pt 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%
Med. β2 µglobulin (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 4: Patient exposure to treatment with VELCADE during phase 2 and 3 studies

	Phase II VELCADE	Phase III VELCADE	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 *	 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 VELCADE 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 5), 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 VELCADE, 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 VELCADE 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 VELCADE independently of age. Regardless of β2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the VELCADE 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 5: Summary of Disease Outcomes from the Phase III and Phase II studies

	Phase III		**Phase III**		**Phase III**		**Phase II**
	All Patients		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**		**≥2 prior lines**
Time related events	**VELCADE N=333[a]**	**Dex N=336[a]**	**VELCADE N=132[a]**	**Dex N=119[a]**	**VELCADE N=200[a]**	**Dex N=217[a]**	**VELCADE 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 (%)	**VELCADE N=315[c]**	**Dex N=312[c]**	**VELCADE N=128**	**Dex N=110**	**VELCADE N=187**	**Dex N=202**	**VELCADE 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 VELCADE alone were able to receive high-dose dexamethasone in conjunction with VELCADE (see Table 2). The protocol allowed patients to receive dexamethasone if they had had a less than optimal response to VELCADE alone. A total of 74 evaluable patients were administered dexamethasone in combination with VELCADE. Eighteen percent of patients achieved, or had an improved response (MR (11%) or PR (7%)) with combination treatment.

5.2 Pharmacokinetic properties

Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose. 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/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

The mean distribution volume of bortezomib ranged from 1659 liters to 3294 liters following single- or repeat-dose administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. Over a bortezomib concentration range of 0.01 to 1.0 µg/ml, the in vitro protein binding averaged 82.9% in human plasma. The percent of bortezomib bound to plasma proteins was not concentration dependent.

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.
Formal studies in patients with severely impaired renal and hepatic functions have not been conducted to date; consequently caution is recommended when administering bortezomib to these classes of patients (see section 4.4). In the absence of data VELCADE is contraindicated in patients with severe liver impairment (see section 4.3).

5.3 Preclinical safety data

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at concentrations as low as 3.125 µg/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 diarrhea, hematopoietic and lymphatic tissues resulting in peripheral blood cytopenias and 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.

Cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421).
Nitrogen.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Reconstituted solution: 8 hours

6.4 Special precautions for storage

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

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.

6.5 Nature and contents of container

10 ml, type 1, glass vial with a grey bromobutyl stopper and an aluminium seal.

The cap colour of the 10 ml vial is royal blue.

The vial is contained in a transparent blister pack consisting of a tray with a lid.

~~1 vial contains 38.5 mg powder for solution for injection.~~

VELCADE is available in cartons containing 1 single-use vial.

6.6 Special precautions for disposal

For single use only.

VELCADE is a cytotoxic agent. Therefore, as with other potentially toxic compounds, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELCADE SINCE NO PRESERVATIVE IS PRESENT.

VELCADE 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.

When reconstituted, each vial of 3.5 mg of VELCADE yields a solution with a concentration of 1 mg/ml. The contents of each 10 ml vial must be reconstituted with 3.5 ml of 9 mg/ml (0.9%) sodium chloride for injection. 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.

Procedure for proper disposal

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

EU/1/04/274/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 26/04/2004

10. DATE OF REVISION OF THE TEXT

21st April 2008

PACKAGE LEAFLET: INFORMATION FOR THE USER

VELCADE 3.5 mg powder for solution for injection

bortezomib

Read all of this leaflet carefully before a doctor gives this medicine to you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious or if you notice any other side effects, please tell your doctor or pharmacist.

In this leaflet **Page**

1. WHAT VELCADE IS AND WHAT IT IS USED FOR

VELCADE belongs to a group of medicines called cytotoxic medicinal products. These are used to kill cancer cells.

VELCADE is used for the treatment of adults with cancer of the bone marrow (multiple myeloma). It is prescribed for patients who have received at least one prior treatment and whose disease is worsening on their last treatment. VELCADE should be used for patients who have already undergone or who cannot undergo bone marrow transplantation.

2. BEFORE YOU ARE GIVEN VELCADE

Your doctor will examine you and take your medical history. You have to give blood samples before and during your treatment with VELCADE.

You must not receive VELCADE:
- if you are allergic (hypersensitive) to the active substance or to any of the other ingredients of VELCADE.
- if you have severe liver problems.
- if you have ongoing history of certain severe pulmonary or heart problems (acute diffuse infiltrative pulmonary and pericardial disease).

Take special care with VELCADE if any of the points in this list applies to you. **Inform** your doctor or nurse:
- if you have a **low level of red blood cells, platelets, or white blood cells**, as these conditions may become worse during treatment with VELCADE.
- if you are suffering from **diarrhoea, constipation, nauseas or vomiting**, as this may become worse during VELCADE treatment.
- if you have a history of **fainting, dizziness or lightheadedness.**
- if you have any problems with your **kidneys.**
- if you have any problems at all with your **liver.**
- if you have had any problems in the past with **numbness, tingling, or pain in the hands or feet** (neuropathy). This effect may become worse during VELCADE treatment.
- if you have had any **bleeding problems.**

- if you have any problems with your **heart or with your blood pressure.**
- if you have been diagnosed in the past with a condition called **amyloidosis.**
- if you have experienced or have **new or increased shortness of breath or cough.** Your doctor may order a chest x-ray to determine if further action is required.

The experience in children and adolescents is limited. Therefore, VELCADE should not be used in this age group.

Using other medicines

Please tell your doctor, medical health personnel or pharmacist about **all** medicines you are taking or have recently taken, whether prescribed for you or bought without a prescription.

Contraception

Both men and women must ensure that contraceptive precautions are taken whilst receiving VELCADE, and for 3 months after treatment.

Pregnancy and breast-feeding

It is advised that you are not given VELCADE if you are pregnant. You must make sure that you do not become pregnant while receiving VELCADE, but if you do, inform your doctor immediately.

It is advised that you do not breast feed while you are receiving VELCADE. If you wish to restart breast-feeding after your VELCADE treatment, you must discuss this with your doctor or nurse, who will tell you when it is safe to do so.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

VELCADE might cause low blood pressure that may lead to tiredness, dizziness, fainting, or blurred vision. Do not drive or operate any dangerous tools or machines if you experience such side effects. Even if you have not felt these effects, you must still be cautious.

3. HOW VELCADE IS GIVEN TO YOU

Your treatment with VELCADE will take place in a specialised medical unit, under the supervision of a doctor experienced in the use of cytotoxic medicinal products.

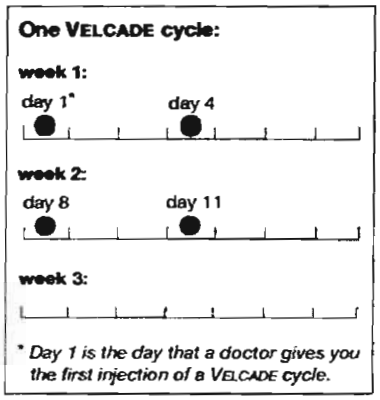
The powder for solution will be dissolved in 9 mg/ml (0.9%) sodium chloride (salt) for injection. The reconstituted solution is injected into a vein.

The dose will be calculated from your height and weight. The usual starting dosage is 1.3 milligrams per square meter body surface area. The injection will take 3 to 5 seconds, and the injection syringe will then be rinsed through with a small quantity of sterile, sodium chloride (salt) solution.

Frequency of treatment

One cycle of treatment with VELCADE consists of a total of 4 doses and will be given over 3 weeks. Doses are given on days 1, 4, 8 and 11, followed by a 10-day break from the treatment.

Your doctor may change the dosage during the treatment, and will decide the total number of cycles that you need. It all depends on your response to the treatment.



4. POSSIBLE SIDE EFFECTS

Like all medicines, VELCADE can cause side effects. If you experience any of the following, inform your doctor or nurse as soon as possible. Some of these effects may be serious. However, there might be ways to reduce the discomfort of these effects.

The side effects in this section are given with an estimation of the frequency with which they may occur. For this purpose, the following frequency categories and denominations have been used:
Very common: side effects which may occur in more than 1 in 10 patients
Common: side effects which may occur in more than 1 in 100 patients and less than 1 in 10 patients.
Uncommon: side effects which may occur in more than 1 in 1000 patients and less than 1 in 100 patients.
Very rare: side effects which may occur in less than 1 in 10,000 patients

Treatment with VELCADE is very commonly associated with toxicities of the blood. The most common blood toxicity is temporary low platelets, therefore you may be more prone to bruising, or bleeding without obvious injury (e.g. bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver). Moreover, you may experience reduction in the number of red or white blood cells, which may lead to anaemia and/or to infections or flu like symptoms.

Treatment with VELCADE is very commonly associated with nerve damage potentially reversible, therefore you may experience numbness, tingling or burning sensation of the skin, or pain in the hands or feet, or weakness. In addition you could experience diarrhoea, severe constipation, or light headedness on standing suddenly (due to drop in blood pressure) which may lead to fainting. In case of diarrhoea it is important to drink more water than usual and your doctor may give you another medicine to control symptoms.

Treatment with VELCADE can be associated with new or increased shortness of breath or cough and your doctor may order a chest x-ray to determine if further action is required.

Other possible side effects:

- Very CommonSensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet
- Reduction in the number of red or white blood cells, anaemia caused by destruction of red blood cells
- Fever, shivering fits
- Shortness of breath without exercise
- Feeling sick in the stomach or vomiting, loss of appetite
- Constipation with or without bloating,
- Diarrhoea, if this happens, it is important to drink more water than usual. Your doctor may give you another medicine to control diarrhoea while you are receiving VELCADE
- Tiredness
- Loss of appetite
- Headache

Common

- Sudden fall of blood pressure on standing which may lead to fainting
- Depression which may be severe, confusion
- Swelling around the eyes or face (which may rarely be due to a serious allergic reaction), or swelling in the ankles, wrists, arms or legs.
- You may be more prone to infections or flu-like symptoms
- General ill feeling, dizziness, light headedness, or a feeling of weakness
- Changes in potassium in your blood, too much sugar in your blood
- Chest pains or coughing with phlegm, shortness of breath with exercise
- Different types of rash and/or itching, lumps on the skin or dry skin
- Redness of the skin or redness and pain at the injection site
- Dehydration
- Heart burn , bloating, belching, wind or stomach pain
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle or bone pain, pain in your limbs or back
- Blurred vision
- Nose bleeds
- Difficulty in sleeping, sweating, anxiety
- Overtiredness

Uncommon

- Palpitations (sensation of rapid or irregular heart beat), changes in heart beat, heart failure, heart attack, chest pain, chest discomfort or decreased ability of the heart to work
- You may experience bleeding from your bowels or stomach, bloody stools, bleeding in the brain, bleeding from the liver or bleeding from mucosal membranes e.g. mouth
- Paralysis, seizures
- Breathing becomes shallow, difficult or stops, wheezing, difficulty in breathing, cough that produces frothy sputum that may be tinged with blood or coughing blood
- Producing much more urine than usual or producing much less urine than usual (kidney damage), painful passing of urine or blood/proteins in the urine
- Yellow discolouration of eyes and skin (jaundice)
- Loss of attention, restlessness or agitation, or you may notice changes in your mental status, mood swings
- Facial blushing or tiny broken capillaries
- Hearing loss, deafness or ringing in the ears
- Changes in calcium, sodium, magnesium, and phosphates in your blood, too little sugar in your blood

- Hormone abnormality affecting salt and water absorption
- Irritated eyes, excessively wet or dry eyes, discharge from the eyes, abnormal vision, eye infections (including herpes zoster), bleeding of the eye or sensitivity to light
- Swelling of your lymph nodes
- Joint or muscle stiffness, muscle spasms or twitching, pain in your bottom
- Hair loss
- Allergic reactions
- Mouth pain, retching, abdominal pain
- Weight increased

Very rare
Inflammation of the lining around your heart

If you notice any other effects not mentioned in this leaflet, inform your doctor or pharmacist.

5. HOW TO STORE VELCADE

Keep out of the reach and sight of children.

Do not store above 30°C. Keep the container in the outer carton in order to protect from light.
Do not use after the expiry date stated on the vial and the carton.

The reconstituted solution may be stored 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.

VELCADE will be stored in the pharmacy

6. FURTHER INFORMATION

What VELCADE contains
- The active substance is bortezomib. Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester). After reconstitution, 1 ml of solution for injection contains 1 mg bortezomib.
- The other ingredients are Mannitol (E 421) and Nitrogen.

What VELCADE looks like and contents of the pack
VELCADE 3.5 mg powder for solution for injection is a white to off-white cake or powder.
Each carton of VELCADE 3.5 mg powder for solution for injection contains a 10 ml glass vial with a royal blue cap, in a transparent blister pack.

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This leaflet was last approved in 04/2008

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. The European Medicines Agency (EMEA) will review any new information which may become available every year and this leaflet will be updated as necessary.

INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

1. Preparation

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

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELCADE SINCE NO PRESERVATIVE IS PRESENT.

1. Preparation of the 3.5 mg vial
   Add 3.5 ml of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the VELCADE powder. The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

2. Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the reconstituted product should be discarded.

3. The reconstituted product is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability 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.

Note: If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

A vial is for single use only and remaining solution must be discarded.

4. Give this leaflet to the patient.

2. Administration

1. Check the dose in the syringe.
2. Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
3. 3Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9%) sodium chloride solution.

3. Disposal

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