SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VELTEZO 3.5 mg I.V./S.C. powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each vial contains 3.5 mg bortezomib.

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

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

Excipient(s):

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White lyophilised powder,

The reconstituted solution is a clear, visibly particle-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In multiple myeloma, patients over 65 years of age who do not have a chance for autologous transplantation or in patients with multiple myeloma with the 13th deletion, thalidomide or VELTEZO (bortezomib) with an appropriate combination chemotherapy scheme can be added in the first step in addition to the multi-agent chemotherapy scheme.

In all other multiple myeloma patients, when disease progression develops after at least 2 cycles of VAD and/or melphalan/prednisone treatment, thalidomide or VELTEZO (bortezomib) treatments can be started.

Appropriate patients should be evaluated in terms of high-dose therapy applications.

VELTEZO (bortezomib) is indicated for the treatment of patients with relapsed or treatment-resistant mantle cell lymphoma who have received at least one of the appropriate doses and duration of prior treatment with an anthracycline and/or alkylating agent or combinations of these treatments with rituximab.

4.2 Posology and method of administration

Treatment should be initiated and administered by a physician who is specialized and experienced in the use of chemotherapeutic agents. The reconstitution of VELTEZO should be done by healthcare professionals.

VELTEZO 3.5 mg powder for solution for injection can be administered intravenously or subcutaneously.

VELTEZO should not be administered by other routes. Intrathecal administration resulted in death.

Posology/administration frequency and period:
Monotherapy
It is recommended to administer VELTEZO at a dose of 1.3 mg/m^2 twice a week (days 1, 4, 8 and 11) for two weeks, followed by a 10-day rest period (days 12-21). This three-week period should be taken as a treatment cycle. An interval of at least 72 hours should be allowed between successive doses of VELTEZO.

It is recommended that patients with confirmed complete remission receive 2 additional cycles of VELTEZO after confirmation of complete remission. It is also recommended that patients who do not achieve complete remission during treatment with VELTEZO continue treatment with VELTESZO until they have had a total of 8 cycles.

Information on retreatment with VELTEZO is limited.

Dose modification and re-initiation of treatment:
VELTEZO treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see section 4.4). Once the symptoms of the toxicity have resolved, VELTEZO 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). Discontinuation of VELTEZO should be considered if symptoms of toxicity do not improve at the lowest dose and the benefit is not significantly greater than the potential 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 VELTEZO only after careful risk/benefit assessment

Table 1: Recommended dose modifications for VELTEZO related neuropathic pain and/or peripheral sensory or motor neuropathy

Severity of neuropathy	**Dosage and scheme modification**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce VELTEZO to 1.0 mg/m^2 or Change VELTEZO treatment schedule to 1.3 mg/m^2 once per week

Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold VELTEZO treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELTEZO treatment and reduce dose to 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy.	Discontinue VELTEZO

* Based on posology modifications in Phase II and III multiple myeloma studies and post-marketing experience. Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.

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

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

Additional information for special populations:

Hepatic impairment:

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended VELTEZO dose. Patients with moderate or severe hepatic impairment should be started on VELTEZO at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability (see Table 2 and sections 4.4 and 5.2).

Table 2: Recommended starting dose modification for VELTEZO in patients with hepatic impairment

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) Levels**	**Modification of starting dose**
Mild	≤ 1x ULN	> ULN	No dosage adjustment needed
	> 1x-1,5x ULN	Any	No dosage adjustment needed
Moderate	> 1,5x-3x ULN	Any	Reduce VELTEZO to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	>3x ULN	Any	

SGOT= serum glutamic oxaloacetic transaminase; AST= aspartate aminotransferase;
ULN= upper limit of the normal range.
* Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

Renal impairment:

The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance > 20 ml/min/1.73 m^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 (Creatinine Clearance < 20 ml/min/1.73 m^2). Since dialysis may reduce bortezomib concentrations, VELTEZO should be administered after the dialysis procedure (see section 5.2).

Paediatric population:
The safety and efficacy of VELTEZO in children below 18 years of age have not been established (see sections 5.1 and 5.2).

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

Combination therapy with melphalan and prednisone:
VELTEZO (bortezomib) is administered in combination with oral melphalan and oral prednisone over nine treatment cycles, as shown in Table 3. A 6-week period is considered a treatment cycle. In Cycles 1-4, VELTEZO is administered twice weekly (on days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELTEZO is administered once weekly (on 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 VELTEZO treatment cycle. At least 72 hours should elapse between consecutive doses of VELTEZO.

Table 3: Recommended posology for VELTEZO when used in combination with melphalan and prednisone in patients with previously untreated multiple myeloma

Twice weekly VELTEZO (Cycles 1-4)													
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vt(1,3mg/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 VELTEZO (Cycles 5-9)													
Hafta	**1**				**2**		**3**	**4**		**5**		**6**
Vt(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
Vt = VELTEZO; M = melphalan, P = prednisone													

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

Prior to initiating a new cycle of therapy:
- Platelet counts should be ≥ 70 x 10^9/L, ANC (absolute neutrophils count) should be ≥ 1 x 10^9/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 4: Dose modifications between subsequent cycles

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

For additional information concerning melphalan and prednisone, see the Summary of Product Characteristics.

Administration method:
Intravenous injection:
VELTEZO 3.5 mg is administered as 3-5 second bolus injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 0.9% solution for injection. At least 72 hours should elapse between consecutive doses of VELTEZO.
Subcutaneous injection:

VELTEZO 3.5 mg reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be administered subcutaneously at an angle of 45-90 degrees. Injection sites should be rotated for successive injections.

If a local injection site reaction occurs after subcutaneous administration of VELTEZO, either a less concentrated VELTEZO solution (VELTEZO 3.5 mg to be constituted to 1 mg/ml instead of 2.5 mg/ml) or a switch to intravenous injection is recommended.

4.3 Contraindications

VELTEZO is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.
It is contraindicated in patients with acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

Intrathecal administration:
There have been fatal cases of inadvertent intrathecal administration of VELTEZO. VELTEZO 3.5 mg powder for solution for injection can be used for intravenous or subcutaneous injection. VELTEZO should not be administered intrathecally.

Gastrointestinal toxicity:
Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with VELTEZO treatment. Cases of ileus have been uncommonly reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity:
VELTEZO treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In a phase 3 study comparing bortezomib (injected intravenously) and dexamethasone, the most common haematological toxicity was transient thrombocytopenia. In a phase 2 study performed, platelets were found to be at their lowest on the 11th day of each bortezomib treatment cycle. There was no evidence of cumulative thrombocytopenia, including the follow-up study of the phase 2 study. The lowest platelet count measured was approximately 40% of baseline. In patients with advanced multiple myeloma, severity of thrombocytopenia was related to pretreatment values: 90% of 21 patients with baseline platelet counts <75,000/µL had their platelet counts decreased to 25,000/µL or less during the study (including 14% who went down to less than 10,000/µL); in contrast, only 14% of 309 patients with baseline platelet counts 75, 000/µL had a platelet count of 25 x 10^9/L or less during the study. Platelet counts should be monitored prior to each dose of bortezomib. When the platelet count is <25,000/µL (<30,000/µL when combined with melphalan and prednisone), bortezomib therapy should be stopped and restarted at a reduced dose (see section 4.2). The potential benefits of treatment should be carefully weighed against the risks, especially the risk factors for moderate to severe thrombocytopenia and bleeding.

Therefore, the differential complete blood count (CBC), including platelet values, should be monitored frequently during treatment with VELTEZO.

Herpes zoster virus reactivation:
Antiviral prophylaxis is recommended in patients being treated with VELTEZO. In the Phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with Bortezomib+ Melphalan+Prednisone compared with Melphalan+Prednisone (14% versus 4% respectively).

Peripheral neuropathy
Treatment with VELTEZO 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 five.

Patients should be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

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

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the VELTEZO dose, schedule or route of administration to subcutaneous (see section 4.2). In a phase 3 multiple myeloma study comparing bortezomib (intravenously administered) and dexamethasone, 51% of patients with ≥ Stage 2 peripheral neuropathy reported improvement or resolution of peripheral neuropathy with supportive care and other treatments. In the phase 2 bortezomib (intravenously administered) trials, improvement or recovery was reported in 71% of patients who discontinued treatment for peripheral neuropathy or had ≥ Stage 3 peripheral neuropathy.

In addition to peripheral neuropathy, autonomic neuropathy may contribute to adverse reactions such as postural hypotension and severe constipation with bowel obstruction. Data on autonomic neuropathy and the contribution of autonomic neuropathy to adverse effects are limited.

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

Hypotension:
Bortezomib treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate and are observed throughout treatment. Patients who developed orthostatic hypotension during bortezomib treatment (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with bortezomib. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

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

Heart failure
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. In the phase 3 randomized controlled comparative study, the incidence of heart failure in the bortezomib (injected intravenously) group was similar to that seen 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.
Electrocardiogram investigations
There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

Pulmonary disorders
There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib (see section 4.8). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.
In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing VELTEZO therapy.
In a clinical trial, two patients (out of 2) given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

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

Hepatic impairment
Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatic reactions
Rare cases of hepatic failure have been reported in patients receiving concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section 4.8)

Tumour lysis syndrome
Because bortezomib is a cytotoxic agent and can rapidly kill malignant cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Concomitant medicinal products
Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see section 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 metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% ($CI_{90\%}$ [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib, there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib, showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers is not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort (St. John's Wort).

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

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

During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents

receiving VELTEZO treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

The effect of dexamethasone, a weaker CYP3A4 inducer, was also evaluated in the same drug-drug interaction study. Based on data from seven patients, there was no significant effect on bortezomib pharmacokinetics.

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

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

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: D

Women of childbearing potential/Contraception

There are no clinical data on exposure to bortezomib during pregnancy. Patients should be counseled to use effective contraceptive measures to prevent pregnancy. Both male and female patients should ensure that they take all contraceptive precautions while using VELTEZO or for up to 3 months after treatment.

Pregnancy

The teratogenic potential of bortezomib has not been fully investigated.

In non-clinical studies, bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of bortezomib on parturition and post-natal development were not conducted (see section 5.3). VELTEZO should not be used during pregnancy unless the clinical condition of the woman requires treatment with VELTEZO. If VELTEZO 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.

Lactation

It is not known whether bortezomib is excreted in human breast milk. Because of the potential for serious adverse reactions in breastfed infants, female patients should be counseled not to breastfeed their infants during treatment with VELTEZO.

Reproductive ability / Fertility
Fertility studies were not conducted with bortezomib (see section 5.3).

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

4.8 Undesirable effects
Summary of the safety profile:
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.

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

The undesirable effects listed below are those considered by the investigators to be causally related or likely to be related to bortezomib. Adverse events were from an integrated data set of 3,628 patients, of whom 2,606 were treated with bortezomib at a dose of 1.3 mg/m^2. The distribution of these 2,606 patients who received bortezomib is as follows:

- 2,068 multiple myeloma patients in whom bortezomib was used as the sole intravenous agent
- 369 multiple myeloma patients receiving bortezomib intravenously in combination with melphalan and prednisone
- 147 patients with multiple myeloma in whom bortezomib was administered subcutaneously as a single agent
- 22 patients with B-cell chronic lymphocytic leukemia (CLL) in whom bortezomib was used as the sole intravenous agent

Bortezomib has been used in the treatment of a total of 2,584 patients with multiple myeloma.

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. Version 13.1 of the MedDRA has been used in defining the advers reactions. Post-marketing adverse reactions not seen in

clinical trials are also included.

Infections and infestations

Common:	Herpes zoster (including disseminated and ophthalmic), pneumonia*, herpes simplex*, fungal infection*
Uncommon:	Sepsis*, bronchopneumonia, herpes virus infection*, bacteraemia (including staphylococcal), hordeolum, influenza, cellulitis, medical device related infection, skin infection*, ear infection*, tooth infection*
Rare:	Meningitis (including bacterial), Epstein-Barr virus infection, erysipelas, genital herpes, staphylococcus infection, tonsillitis, varicella, mastoiditis, post viral fatigue syndrome, progressive multifocal leukoencephalopathy

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon:	Malign neoplazm
Rare:	Plasmastic leukemia, renal cell carcinma, mass, mycosis fungoides, bening neoplazm

Blood and lymphatic system disorders

Very Common:	Thrombocytopenia*, neutropenia*, anaemia*, leucopenia
Common:	Lymphopenia*
Uncommon:	Pancytopenia*, febrile neutropenia, coagulopathy*, leukocytosis*, lymphadenopathy
Rare:	Hyperviscosity syndrome, thrombocytopenia purpura*, blood disorders, haemorrhagic diathesis, lenfocytic infiltration

Immune system disorders

Uncommon:	Hypersensitivity*
Rare:	Anaphylactic shock, Type III immune complex mediated reaction

Endocrine disorders

Uncommon:	Hyperthyroidism*, inappropriate antidiuretic hormone (ADH) secretion
Rare:	Cushing sendrom*, hypothyroidism

Metabolism and nutrition disorders

Very common:	Decreased appetite
Common:	Electrolyte imbalance*, dehydration, enzyme abnormality*, hyperuricemia*
Uncommon:	Tumor lysis syndrome, failure to thrive*, hypoglycaemia*, hyperglycaemia, hypoproteinaemia*, fluid retention, hypovolaemia
Rare:	Acidosis, fluid overload, hypochloremia*, diabetes mellitus*, hyperproteinemia*, hypouricemia*, metabolic disease, vitamin B

complex deficiency, vitamin B12 deficiency, gout, hyperammonemia*, increased appetite, alcohol intolerance

Psychiatric disorders

Common:	Mood disorders and disturbances*, anxiety disorder*, sleep disorder*
Uncommon:	Mental disorder*, hallucinations, confusion*, restlessness
Rare:	Suicidal ideation*, psychotic disorders*, abnormal dreams, adjustment disorder, delirium, decreased libido

Nervous system disorders

Very Common:	Peripheral neuropathy*, peripheral sensory neuropathy*, dysesthesia*, neuralgia*, headache*
Common:	Peripheral motor neuropathy, polyneuropathy, loss of consciousness (including syncope), dizziness*, dysgeusia*, lethargy
Uncommon:	Intracranial hemorrhage*, tremor, peripheral sensorimotor neuropathy, ataxia*, dyskinesia*, memory loss*, encephalopathy*, balance disturbances, neurotoxicity, presyncope, post-herpetic neuralgia, speech disorder*, restless legs syndrome, migraine, sciatica, attention disorder, abnormal reflexes*, parosmia
Rare:	Brain edema, cerebral hemorrhage, transient ischemic attack, autonomic nervous system imbalance, autonomic neuropathy, convulsion, cranial palsy*, paralysis*, paresis*, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorders, motor dysfunction, nervous system disorder, radiculitis, drooling, hypotonia

Eye disorders

Common:	Eye swelling*, vision abnormality*, conjunctivitis*, dry eye*
Uncommon:	Eye haemorrhage*, eyelid infection*, eye inflammation*, ocular hyperemia, diplopia, eye irritation*, eye pain, increased lacrimation, eye discharge
Rare:	Corneal lesion*, exophthalmos, retinitis, scotoma, eye disease (including eyelid), acquired dacryoadenitis, photophobia, photopsia, optic neuropathy#, different degrees of visual impairment (up to blindness)*

Ear and labyrinth disorder

Common:	Vertigo*
Uncommon:	Hearing impaired (up to and including deafness), dysacusis*, tinnitus*, ear discomfort*
Rare:	Ear haemorrhage, ear disorder

Cardiac disorders

Common:	Cardiac failure*, tachycardia*
Uncommon:	Cardiopulmonary arrest*, cardiac fibrillation (including atrial fibrillation), arrhythmia*, palpitations, angina pectoris, pericarditis, cardiomyopathy*, ventricular dysfunction*, bradycardia
Rare:	Atrial flutter, myocardial infarction*, atrioventricular block*, cardiovascular disease (including cardiogenic shock), Torsade de pointes, unstable angina, coronary artery failure, left ventricular failure, mitral valve insufficiency, sinus arrest

Vascular disorders

Common:	Hypotension*, orthostatic hypotension, hypertension*
Uncommon:	Deep vein thrombosis*, haemorrhage*, thrombophlebitis (including superficial), circulatory collapse (including hypovolemic shock), phlebitis, flushing, haematoma*, poor peripheral circulation, hot flushes, vasculitis, pallor
Rare:	Peripheral embolism, lymphoedema, erythromelalgia, vasodilation, vein discolouration, venous insufficiency

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnea*, epistaxis, upper/lower respiratory tract infection*, cough*
Uncommon:	Pulmonary embolism, pleural effusion, pulmonary edema (including acute), bronchospasm, chronic obstructive pulmonary disease*, hypoxemia, pulmonary hypertension, airway congestion*, hypoxia, pleurisy*, pulmonary fibrosis, hiccups, rhinorrhea, dysphonia, wheezing
Rare:	Respiratory failure, acute respiratory distress syndrome, apnea, pneumothorax, atelectasis, hemoptysis, hyperventilation, orthopnea, tachypnea, pneumonia, respiratory alkalosis, hypocapnia*, interstitial lung disease, lung infiltration, throat tightness, throat dryness, bronchial hyperactivity, increased upper airway secretion, throat irritation

Gastrointestinal disorders

Very Common:	Vomiting, diarrhea*, nausea, constipation, abdominal pain (including gastrointestinal pain)*
Common:	Gastrointestinal haemorrhage (including mucosal)*, dyspepsia, stomatitis*, abdominal tension, oropharyngeal pain*, abdominal discomfort, oral disorder*, flatulence
Uncommon:	Pancreatitis (including chronic), hematemesis, lip swelling*, oral ulceration*, ileus*, enteritis*, gastritis*, gingival bleeding, gastroesophageal reflux disease*, gastrointestinal inflammation*, dysphagia, irritable bowel syndrome, esophagitis, gastrointestinal

	disorder, vomiturition, gastrointestinal motility disorder*, salivary glands disease*, oropharyngeal blistering*
Rare:	Acute pancreatitis, peritonitis*, tongue edema*, ascites, cheilitis, fecal incontinence, anal sphincter atony, fecaloma, rectal discharge, lip pain, periodontitis, anal fissure, change in bowel habits, proctalgia, abnormal faeces

Hepatobiliary disorders

Common:	Hepatic enzyme abnormality*
Uncommon:	Hepatotoxicity (including liver disorder), hepatitis*, cholestasis
Rare:	Hepatic failure, hepatomegaly, Budd-Chiari syndrome, hepatic hemorrhage, cholelithiasis.

Skin and subcutaneous tissue disorders

Very common:	Rash*
Common:	Urticaria, pruritus*, erythema, dermatitis*, dry skin
Uncommon:	Acute febrile neutrophilic dermatosis, toxic skin eruption, hair disorder*, petechiae, ecchymosis, skin lesion, purpura, skin nodule*, psoriasis, palmar-plantar erythrodysaesthesia syndrome, hyperhidrosis, night sweats, acne*, bloody blisters, pigmentation disorder *, nail disorder
Rare:	Erythema multiforme, skin reaction, Jessner lymphocytic infiltration, subcutaneous hemorrhage, Livedo reticularis, skin induration, blistering, cold sweat, papule, photosensitivity reaction, seborrhea, skin disorder

Musculoskeletal and connective tissue disorders

Very Common:	Musculoskeletal pain*
Common:	Muscle spasms*, pain in extremity, muscle weakness
Uncommon:	Muscle twitching, joint swelling, arthritis*, joint stiffness, myopathy*, sensation of heaviness
Rare:	Rhabdomyolysis,temporomandibular joint syndrome, fistula, joint swelling, jawbone pain, bone disorder, dactylitis, synovial cyst

Renal and urinary disorders

Common:	Renal impairment*, chronic renal failure*
Uncommon:	Acute renal failure, urinary tract infection*, hematuria*, urinary retention, dysuria*, micturition disorder*, proteinuria, azotemia, oliguria*, pollakiuria
Rare:	Renal colic, bladder irritation, abnormal urine odor

Reproductive system and breast disorders

Uncommon:	Vaginal haemorrhage, genital pain*, erectile dysfunction, testicular disorder*
Rare:	Prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration

Congenital, familial/ genetic disorders

Rare:	Aplasia, gastrointestinal malformation, ichthyosis

General disorders and administration site conditions

Very common:	Pyrexia*, fatigue, asthenia
Common:	Edema (including peripheral), chills, pain*, injection site reaction*, malaise*
Uncommon:	Death (including sudden death), general physical health deterioration*, facial edema*, chest pain, mucosal disorder*, gait disturbance, feeling cold, extravasation*, catheter-related complications*, thirst, chest discomfort, feeling of body temperature change* , injection site pain *
Rare:	Injection site hemorrhage*, hernia*, injection site phlebitis*, delayed wound healing, inflammation, tension, ulcer, irritability, non-cardiac chest pain, catheter site pain, foreign body sensation

Investigations

Common:	Weight decreased
Uncommon:	Hyperbilirubinaemia*, pyrexia, C-reactive protein increased
Rare:	Megacaryocyte decrease, PO_2 increase, blood bicarbonate decreased, blood creatinine increased*, electrocardiogram abnormalities, INR abnormal, increase in beta 2 microglobulin levels, blood creatinine decreased, positive cytomegalovirus test, decrease in gastric pH, increase in thrombocyte aggregation, increase in troponin I level, decrease in blood testesterone level, proteinuria, increase in serum ferritine level, increase in urine pH

Injury and poisoning

Uncommon:	Fall, contusion
Rare:	Cranial fractures, transfusion reaction, rigors*, face injury, joint injury, laceration, procedural pain, radiation injuries*

Surgical and medical procedures

Rare:	Macrophage activation

*: Grouping of more than one MedDRA preferred term.
#: Post-marketing adverse reaction regardless of indication

Description of selected adverse reactions:
Herpes zoster virus reactivation
Antiviral prophylaxis was administered to 26% of the patients in the bortezomib+melphalan+prednisone arm. The incidence of herpes zoster among patients in the bortezomib+melphalan+prednisone treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Notable differences in the safety profile of bortezomib administered subcutaneously versus intravenously as single agent:
In the Phase 3 study patients who received bortezomib subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity, and a 5% lower incidence of discontinuation of bortezomib. The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were 12%-15% lower in the subcutaneous group than in the intravenous group. In addition, the incidence of Grade 3 or higher peripheral neuropathies was 10% lower, and the discontinuation rate due to peripheral neuropathies 8% lower for the subcutaneous group as compared to the intravenous group

A local adverse reaction, mostly redness, was observed in 6% of patients receiving subcutaneous administration. The cases showed improvement in an average of 6 days, and dose adjustment was required in two patients. In two of the patients, 1% (1 case with pruritus and 1 case with redness), the reactions were severe.

While the mortality rate during the treatment was 5% in patients who received subcutaneous administration, this rate was 7% in the group that received intravenous administration. While death due to progressive disease was 18% in patients who received subcutaneous administration, this rate was 9% in the group that received intravenous administration.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose
In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies, see section 5.3.

There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents
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 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a t½ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including (but not limited to) altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth in vivo in many preclinical tumour models, including multiple myeloma.

Data from *in vitro, ex-vivo,* and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib

Clinical efficacy in previously untreated multiple myeloma

A prospective Phase III, international, randomised (1:1), open-label clinical study (VISTA) of 682 patients was conducted to determine whether bortezomib (1.3 mg/m^2 injected intravenously) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/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. The median age of the patients in the study was 71 years, 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80. Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/L, and a median platelet count of 221.5 x 10^9/L. Similar proportions of patients had creatinine clearance ≤ 30 ml/min (3% in each arm).

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the melphalan+prednisone arm were offered bortezomib+melphalan+ prednisone treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up of 60.1 months. A statistically significant survival benefit in favour of the bortezomib+ melphalan+ prednisone treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies including bortezomib-based regimens. Median survival for the bortezomib+melphalan+prednisone treatment group was 56.4 months compared to 43.1 for the melphalan+prednisone treatment group. Efficacy results are presented in Table 6:

Table 6: Efficacy results following the final survival update to VISTA study

Efficacy endpoint	**B+M+P n=344**	**M+P n=338**
Time to progression Events n (%)	101 (29)	152 (45)
Median[a] (%95 CI)	20,7 months (17.6, 24.7)	15 months (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 months (16.6, 21.7)	14 months (11.1, 15)
Hazard ratio[b] (%95 CI)	0.61 (0.49, 0.76)	
p-value[c]	0.00001	
Overall survival *		

Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (%95 CI)	56.4 ay (52.8, 60.9)	43.1 ay (35.3, 48.3)
Hazar ratio[b] (%95 CI)	0.695 (0.567, 0.852)	
p-değeri[c]	0.00043	
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 ay	4.2 ay
Median[a] response duration		
CR[f]	24 months	12.8 months
CR + PR[f]	19.9 months	31.1 months
Time to next therapy Events n (%)	224 (65.1)	260 (76.9)
Efficacy endpoint	**B+M+P n=344**	**M+P n=338**
Median[a] (%95 CI)	27 ay (24.7, 31.1)	19,2 ay (17, 21)
Hazard ratio[b] (%95 CI)	0.557 (0.462, 0.671)	
p-value[c]	<0,000001	

[a] Kaplan-Meier estimate.

[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors β2-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 β2-microglobulin, albumin, and region

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

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

[f] CR=Complete Response; PR=Partial Response. EBMT criteria

[g] All randomised patients with secretory disease

* Survival update based on a median duration of follow-up at 60.1 months mo: months CI=Confidence Interval

Clinical efficacy in relapsed or refractory multiple myeloma
The safety and efficacy of bortezomib (injected intravenously) were evaluated in 2 studies at the recommended dose of 1.3 mg/m^2: a Phase 3 randomised, comparative study (APEX), versus dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a Phase 2 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

In the Phase III study, treatment with bortezomib led to a significantly longer time to progression, asignificantly prolonged survival and a significantly higher response rate, compared to treatment withdexamethasone (see Table 7), in all patients as well as in patients who have received 1 prior line oftherapy. As a result of a pre-planned interim analysis, the dexamethasone arm was halted at the recommendation of the data monitoring committee and all patients randomized to dexamethasone were than offered bortezomib, regardless of disease status. Due to this early crossover, the median durationof follow-up for surviving patients is 8.3 months. Both in patients who were refractory to their lastprior 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 β2-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 7: Summary of disease outcomes from the Phase III (APEX) 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	**B n=333[a]**	**Dex n=336[a]**	**B n=132[a]**	**Dex n=119[a]**	**B n=200[a]**	**Dex n=217[a]**	**B n=202[a]**
TTP, day (%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 (%)	**B n=315[c]**	**Dex n=312[c]**	**B n=128**	**Dex n=110**	**B n=187**	**Dex n=202**	**B 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]	58 (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 period Days (months)	242 (8)	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 medicinal product.

[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

TTP-Time to Progression

CI=Confidence Interval

B=Bortezomib; Dex=dexamethasone

CR=Complete Response; nCR=near Complete response

PR=Partial Response; MR=Minimal response

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. 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.

Clinical efficacy with subcutaneous administration of bortezomib in patients with relapsed/refractory multiple myeloma
An open label, randomised, Phase III non-inferiority study compared the efficacy and safety of the subcutaneous administration of bortezomib versus the intravenous administration. This study included 222 patients with relapsed/refractory multiple myeloma, who were randomised in a 2:1 ratio to receive 1.3 mg/m^2 of bortezomib by either the subcutaneous or intravenous route for 8 cycles.

Patients who did not obtain an optimal response (less than Complete Response [CR]) to therapy with bortezomib alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and after bortezomib administration. Patients with baseline Grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/ µL were excluded. A total of 218 patients were evaluable for response.

This study met its primary objective of non-inferiority for response rate (CR+PR) after 4 cycles of single agent bortezomib for both the subcutaneous and intravenous routes, 42% in both groups. In addition, secondary response-related and time to event related efficacy endpoints showed consistent results for subcutaneous and intravenous administration (Table 8).

Table 8: Summary of efficacy analyses comparing subcutaneous and intravenous administrations of bortezomib

	Bortezomib intravenous arm	**Bortezomib subcutaneous arm**
Response Evaluable Population	**n=73**	**n=145**
Response Rate at 4 cycles n (%)		
ORR (CR+PR)	31 (42)	61 (42)
p-value[a]	0.00201	
CR n (%)	6 (8)	9 (6)
PR n (%)	25 (34)	52 (36)
nCR n (%)	4 (5)	9 (6)
Response Rate at 8 cycles n (%)		
ORR (CR+PR)	38 (52)	76 (52)
p-value[a]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29 (40)	61 (42)
nCR n (%)	7 (10)	14 (10)
Intent to Treat Population[b]	**n=74**	**n=148**

TTP, months	9.4	10.4
(%95 CI)	(7.6, 10.6)	(8.5, 11.7)
Hazard ratio (%95 CI)[c]	0.839 (0.564, 1.249)	
p-value[d]	0.38657	
Progression Free Survival, months	8	10.2
(%95 CI)	(6.7, 9.8)	(8.1, 10.8)
Hazar ratio (%95 CI)[c]	0.824 (0.574, 1.183)	
p-value[d]	0.295	
1-year Overall Survival (%)[e]	76.7	72,6
(%95 CI)	(6.1, 85.4)	(63.1, 80)

[a] p-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.

[b] 222 subjects were enrolled into the study; 221 subjects were treated with bortezomib

[c] Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.

[d] Log rank test adjusted for stratification factors: ISS staging and number of prior lines.

[e] Median duration of follow up is 11.8 months

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1 mg/m^2 and 1.3 mg/m^2 dose to 11 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 67-106 ng/ml for the 1 mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m2 dose to patients with multiple myeloma (n=14 in the intravenous group, n=17 in the subcutaneous group), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. The C_{max} after subcutaneous administration (20.4 ng/ml) was lower than intravenous (223 ng/ml). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% and 122.80%.

Distribution

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

Biotransformation:
In vitro studies with human liver microsomes and human c-DNA-expressing P450 isoenzymes indicate that bortezomib is oxidatively metabolized primarily by cytochrome P450, 3A4, 2C19, and 1A2 enzymes. The metabolism of bortezomib by CYP 2D6 and 2C9 enzymes is secondary. The major metabolic pathway is deboronation to form 2 deboronized metabolites, which are then converted by hydroxylation to various metabolites. Deboronized bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination:
The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15-32 L/h and 18-32 L/h following subsequent doses for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively

Linearity / Non-linearity
After intravenous bolus and subcutaneous multiple dose administration of bortezomib at a dose of 1.3 mg/m^2 to patients with multiple myeloma, the total systemic exposure (AUC_{last}) was found to be equivalent for subcutaneous and intravenous administration.

Characteristic properties of patients
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in a Phase I study during the first treatment cycle, including 61 patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m^2.

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored (see section 4.2, Table 2).

Renal impairment
A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 ml/min/1.73 m^2, n=12), Mild (CrCL=40-59 ml/min/1.73 m^2, n=10), Moderate (CrCL=20-39 ml/min/1.73 m^2, n=9), and Severe (CrCL < 20 ml/min/1.73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

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 (CHO) 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 doses, but no direct embryo-foetal toxicity below maternally toxic doses.

Fertility studies were not performed with bortezomib but evaluation of reproductive tissues has been performed in the general toxicity studies. In the six 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 haematopoietic 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 intravenous 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

D-mannitol injectable

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in “Section 6.6 Special precautions for disposal and other handling”.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in room temperature below 25°C in the outer carton in order to protect from light.

VELTEZO should be used immediately after reconstitution. If not used immediately, it can be stored for 8 hours at 25°C stored in the original vial.

6.5 Nature and contents of container
VELTEZO is packaged in sealed vial. Each sealed vial is supplied with leaflet in cardboard box.

6.6 Special precautions for disposal and other handling
General precautions
VELTEZO is an antineoplastic. Therefore, caution should be used during handling and preparation of VELTEZO. Use of gloves and other protective clothing to prevent skin contact is recommended.

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

There have been fatal cases of inadvertent intrathecal administration of bortezomib. VELTEZO 3.5 mg IV/SC powder for injection is for intravenous or subcutaneous use.

VELTEZO must be reconstituted by a healthcare professional.

Reconstitution / Preparation for intravenous injection
Each 10 ml vial of VELTEZO must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes. After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Reconstitution / Preparation for subcutaneous injection
Each 10 ml vial of VELTEZO must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes. After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

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

7. MARKETING AUTHORISATION HOLDER

Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No:1
Küçükçekmece/İSTANBUL
Tel: 0212 692 92 92
Fax: 0212 697 00 24
E-mail: deva@devaholding.com.tr

8. MARKETING AUTHORISATION NUMBER(S)

2018/289

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATIONİlk

Date of first authorisation: 30.05.2018
Date of renewal:

10. DATE OF REVISION OF THE TEXT