SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg bortezomib.

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

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

For the full list of excipients, see section 6.1

3.PHARMACEUTICAL FORM

Powder for solution for injection.

A white to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BORTEZOMIB NEAPOLIS as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

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

BORTEZOMIB NEAPOLIS in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

BORTEZOMIB NEAPOLIS in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation**.**

4.2 Posology and method of administration

Treatment must be initiated under the supervision of a physician experienced in the treatment of cancer patients, however, this medicine may be administered by a healthcare professional experienced in use of chemotherapeutic agents. Bortezomib must be reconstituted by a healthcare professional (see section 6.6).

Posology for treatment of progressive multiple myeloma (patients who have received at least one prior therapy)

Monotherapy

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of bortezomib following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of bortezomib therapy. At least 72 hours should elapse between consecutive doses of bortezomib.

Dose adjustments during treatment and re-initiation of treatment for monotherapy

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

Neuropathic pain and/or peripheral neuropathy

Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1 (see section 4.4). Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

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

Severity of neuropathy	**Posology modification**
Grade 1 (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 bortezomib to 1.0 mg/m^2 or Change bortezomib 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 bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate bortezomib 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 bortezomib

* 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.

Combination therapy with pegylated liposomal doxorubicin

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the bortezomib treatment cycle as a 1 hour intravenous infusion administered after the bortezomib injection.

Up to 8 cycles of this combination therapy can be administered as long as patients have not progressed and tolerate treatment. Patients achieving a complete response can continue treatment for at least 2 cycles after the first evidence of complete response, even if this requires treatment for more than 8 cycles. Patients whose levels of paraprotein continue to decrease after 8 cycles can also continue for as long as treatment is tolerated and they continue to respond.

For additional information concerning pegylated liposomal doxorubicin, see the corresponding Summary of Product Characteristics.

Combination with dexamethasone

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m2 body surface area twice weekly for two weeks on days 1, 4, 8,

and 11 in a 21 day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the bortezomib treatment cycle.

Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.

For additional information concerning dexamethasone, see the corresponding Summary of Product Characteristics.

Dose adjustments for combination therapy for patients with progressive multiple myeloma

For bortezomib dosage adjustments for combination therapy follow dose modification guidelines described under monotherapy above.

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

Combination therapy with melphalan and prednisone

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection in combination with oral melphalan and oral prednisone as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, bortezomib is administered once weekly on days 1, 8, 22 and 29. At least 72 hours should elapse between consecutive doses of bortezomib. Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each bortezomib treatment cycle. Nine treatment cycles of this combination therapy are administered.

Table 2: Recommended posology for bortezomib in combination with melphalan and prednisone

Twice weekly bortezomib (cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
B (1.3 mg/m$^{2)}$	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once weekly bortezomib (cycles 5-9)

Week	**1**	**2**	**3**	**4**	**5**	**6**

B (1.3 mg/m$^{2)}$	Day 1	--	--	--	Day 8	rest period	Day 22	Day 29	rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	rest period	--		rest period

B=bortezomib; 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 and the absolute neutrophils count should be **≥** 1.0 x 10^9/l

• Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Posology modifications during subsequent cycles of bortezomib *therapy in combination with melphalan and prednisone*

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

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

Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)

Combination therapy with dexamethasone

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28 day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib treatment cycle.

Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 4).

Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 4: Posology for bortezomib combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

B+ Dx	**Cycles 1 to 4**				
	Week	**1**	**2**	**3**	
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	
	Dx 40 mg	Day1, 2, 3, 4	Day 8, 9, 10, 11	-	
B+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**4**
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period

	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycles 2 to 4[b]				
	B (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 200 mg[a]	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

B= Bortozemib; Dx=dexamethasone; T=thalidomide

[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.

[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients

For bortezomib dosage adjustments, dose modification guidelines described for monotherapy should be followed.

In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the Summary of Product Characteristics.

Posology for patients with previously untreated mantle cell lymphoma (MCL)

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (BR-CAP)

BORTEZOMIB NEAPOLIS is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Six bortezomib cycles are recommended, although for patients with a response first documented at cycle 6, two additional bortezomib cycles may be given. At least 72 hours should elapse between consecutive doses of bortezomib.

The following medicinal products are administered on day 1 of each bortezomib 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.

Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each bortezomib treatment cycle.

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

Prior to initiating a new cycle of therapy:

• Platelet counts should be ≥ 100,000 cells/µL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/µL

• Platelet counts should be ≥ 75,000 cells/µL in patients with bone marrow infiltration or splenic sequestration

• Haemoglobin ≥ 8 g/dL

• Non-haematological toxicities should have resolved to Grade 1 or baseline.

Bortezomib treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also section 4.4). For dose adjustments, see Table 5 below.

Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 5: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity	
• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/µL	Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL. • If, after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
• If platelet counts < 25,000 cells/µL or ANC <750 cells/µL on a bortezomib dosing day (other than Day 1 of each cycle)	Bortezomib therapy should be withheld
Grade ≥ 3 non-haematological toxicities considered to be related to bortezomib	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or

	better. Then, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib -related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 1.

In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

Special populations

Elderly

There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age with multiple myeloma or with mantle cell lymphoma.

There are no studies on the use of bortezomib in elderly patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Therefore, no dose recommendations can be made in this population.

In a study in previously untreated mantle cell lymphoma patients, 42.9% and 10.4% of patients exposed to bortezomib were in the range 65-74 years and ≥ 75 years of age, respectively. In patients aged ≥ 75 years, both regimens, BR-CAP as well as R-CHOP, were less tolerated (see section 4.8).

Hepatic impairment

Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability (see Table 6 and sections 4.4 and 5.2).

Table 6: Recommended starting dose modification for bortezomib in patients with hepatic impairment

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) levels**	**Modification of starting dose**
Mild	≤ 1.0 x ULN	> ULN	None

	> 1.0 x-1.5x ULN	Any	None
Moderate	> 1.5 x-3x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

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

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

Renal impairment

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

Paediatric population

The safety and efficacy of bortezomib in children below 18 years of age have not been established (see sections 5.1 and 5.2). Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

BORTEZOMIB NEAPOLIS is available for intravenous or subcutaneous administration.

Bortezomib should not be given by other routes. Intrathecal administration has resulted in death.

Intravenous injection

Bortezomib 3.5 mg reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. At least 72 hours should elapse between consecutive doses of bortezomib.

Subcutaneous injection

Bortezomib 3.5 mg reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections.

If local injection site reactions occur following bortezomib subcutaneous injection, either a less concentrated bortezomib solution (bortezomib 3.5 mg to be reconstituted to 1 mg/ml instead of

2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

When bortezomib is given in combination with other medicinal products, refer to the Summary of Product Characteristics of these products for instructions for administration

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4.3 Contraindications

- Hypersensitivity to the active substance, to boron, or to any of the excipients listed in section 6.1.
- Acute diffuse infiltrative pulmonary and pericardial disease.

When BORTEZOMIB NEAPOLIS is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications..

4.4 Special warnings and precautions for use

When bortezomib is given in combination with other medicinal products, the Summary of Product Characteristics of these other medicinal products must be consulted prior to initiation of treatment with bortezomib. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib. BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. BORTEZOMIB NEAPOLIS should not be administered intrathecally.

Gastrointestinal toxicity

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

Haematological toxicity

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with bortezomib and in patients with previously untreated MCL treated with bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single-agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/µl, 90% of 21 patients had a count ≤ 25,000/µl during the study, including 14% <

10,000/µl; in contrast, with a baseline platelet count > 75,000/µl, only 14% of 309 patients had a count ≤ 25,000/µl during the study.

In patients with MCL (study LYM-3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the bortezomib treatment group (BR-CAP) as compared to the non-bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the BR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (BR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the BR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be withheld when the platelet count is < 25,000/µl or in the case of combination with melphalan and prednisone when the platelet count is ≤ 30,000/µl (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.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate (see section 4.2).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the BR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.2).

Herpes zoster virus reactivation

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

In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the BR-CAP arm and 1.2% in the R-CHOP arm (see section 4.8).

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of

hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with bortezomib. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML)

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.

Peripheral neuropathy

Treatment with bortezomib is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

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

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose or schedule of bortezomib or route of administration to subcutaneous (see section 4.2). Neuropathy has been managed with supportive care and other therapies.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving bortezomib in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy.

Special care is required when treating patients with any risk factors for seizures.

Hypotension

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

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Heart failure

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

Electrocardiogram investigations

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

Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib (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 bortezomib therapy.

In a clinical trial, two patients (out of 2) given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (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 bortezomib and concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section 4.8).

Tumour lysis syndrome

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

Concomitant medicinal products

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (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% (CI90% [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

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

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

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

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

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

4.6 Pregnancy and lactation

<u>Contraception in males and females</u>

Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.

Pregnancy

No clinical data are available for bortezomib with regard to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

In non-clinical studies, bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of bortezomib on parturition and post-natal development were not conducted (see section 5.3). Bortezomib should not be used during pregnancy unless the clinical condition of the woman requires treatment with bortezomib. If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of potential for hazard to the foetus.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the thalidomide pregnancy prevention programme are met. Patients receiving bortezomib in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide. Refer to the Summary of Product Characteristics of thalidomide for additional information.

Breast-feeding

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast feeding should be discontinued during treatment with bortezomib.

Fertility

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

4.7 Effects on ability to drive and use machines

Bortezomib may have a moderate influence on the ability to drive and use machines. Bortezomib may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions

Multiple Myeloma

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

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (**≥** 1/10); common (**≥** 1/100 to < 1/10); uncommon (**≥** 1/1,000 to < 1/100); rare (**≥** 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 7 has been generated using Version 14.1 of the MedDRA. Post-marketing adverse reactions not seen in clinical trials are also included.

Table 7: Adverse reactions in patients with Multiple Myeloma treated with bortezomib in clinical trials and all post-marketing adverse reactions regardless of indication[#]

System Organ Class	**Incidence**	**Adverse reaction**
Infections and infestations	Common	Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic[#], Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia[#]
	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombocytopenic purpura, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration, Thrombotic microangiopathy (including Thrombocytopenic purpura)[#]

Immune system disorders	Uncommon	Angioedema#, Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality*
	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc dementia)*, Encephalopathy*, Posterior Reversible Encephalopathy Syndrome#, Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy*, Paralysis*, Paresis*, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia

Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Eye inflammation*, Chalazion[#], Blepharitis[#], Diplopia, Dry eye*, Eye irritation*, Eye pain, Lacrimation increased, Eye discharge
	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy[#], Different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc tinnitus)*, Hearing impaired (up to and inc deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade[#], Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*
	Uncommon	Cerebrovascular accident[#], Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal) *, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage[#], Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper-airway cough syndrome

Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence
	Uncommon	Pancreatitis (inc chronic) *, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic#, Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*
	Rare	Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis#, Stevens-Johnson syndrome#, Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer#, Acne*, Blister*, Pigmentation disorder*
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*, Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations*, Synovial cyst
	Common	Renal impairment*

Renal and urinary disorders	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Pain*, Malaise*
	Uncommon	General physical health deterioration*, Face oedema*, Injection site reaction*, Mucosal disorder*, Chest pain, Gait disturbance, Feeling cold, Extravasation*, Catheter related complication*, Change in thirst*, Chest discomfort, Feeling of body temperature change*, Injection site pain*
	Rare	Death (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia (inc hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*, C-reactive protein increased
	Rare	Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised ratio abnormal*, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology*, Urine analysis abnormal*
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

NOS = not otherwise specified

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication

Mantle Cell Lymphoma (MCL)

The safety profile of bortezomib in 240 MCL patients treated with bortezomib at 1.3 mg/m2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP), versus

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

Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the BR-CAP arm and with at least a possible or probable causal relationship to the components of the BR-CAP arm, are listed in Table 8 below. Also included are adverse drug reactions identified in the BR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to bortezomib based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 8 has been generated using Version 16 of the MedDRA.

Table 8 Adverse reactions in patients with Mantle Cell Lymphoma treated with BR-CAP in a clinical trial

System Organ Class	**Incidence**	**Adverse reaction**
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock) *, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*

Nervous system disorders	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus) *
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the B+M+P arm. The incidence of herpes zoster among patients in the B+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the BR-CAP arm. The incidence of herpes zoster among patients in the BR-CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 4.4).

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

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

Peripheral neuropathy in combination regimens

Multiple Myeloma

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

Table 9: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

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

VDDx=vincristine, doxorubicin, dexamethasone; BDx=bortezomib, dexamethasone; TDx=thalidomide, dexamethasone; BTDx=bortezomib, thalidomide, dexamethasone; PN=peripheral neuropathy

Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma

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

Table 10: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	BR-CAP	R-CHOP
	(N=240)	(N=242)

Incidence of PN (%)		
All GradePN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

BR-CAP= bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PN=peripheral neuropathy

Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients

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

Notable differences in the safety profile of bortezomib administered subcutaneously versus intravenously as single agent

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

Six percent of patients had an adverse local reaction to subcutaneous administration, mostly redness. Cases resolved in a median of 6 days, dose modification was required in two patients. Two (1%) of the patients had severe reactions; 1 case of pruritus and 1 case of redness.

The incidence of death on treatment was 5% in the subcutaneous treatment group and 7% in the intravenous treatment group. Incidence of death from “Progressive disease” was 18% in the subcutaneous group and 9% in the intravenous group.

Retreatment of patients with relapsed multiple myeloma

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation 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 via the national pharmacovigilance System.

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 $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.
Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.
Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.
Data from *in vitro, ex-vivo,* and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical efficacy in previously untreated multiple myeloma

A prospective Phase III, international, randomised (1:1), open-label clinical study (MMY-3002 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 haemoglobin 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 M+P arm were offered B+M+P 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 B+M+P treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies including bortezomib -based regimens. Median survival for the B+M+P treatment group was 56.4 months compared to 43.1 for the M+P treatment group. Efficacy results are presented in Table 11:

Table 11: 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 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free survival Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall survival* Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value[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 mo	4.2 mo
Median[a]response duration		
CR[f]	24.0 mo	12.8 mo
CR+PRf	19.9 mo	13.1 mo
Time to next therapy Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
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: $ß_2$-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP

[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: $ß_2$-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

Patients eligible for stem cell transplantation

Two randomised, open-label, multicenter Phase III trials (IFM-2005-01, MMY-3010) were conducted to demonstrate the safety and efficacy of bortezomib in dual and triple combinations with other chemotherapeutic agents, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma.

In study IFM-2005-01 bortezomib combined with dexamethasone [BDx, n=240] was compared to vincristine- doxorubicin-dexamethasone [VDDx, n=242]. Patients in the BDx group received four 21 day cycles, each consisting of bortezomib (1.3 mg/m^2 administered intravenously twice weekly on days 1, 4, 8, and 11), and oral dexamethasone (40 mg/day on days 1 to 4 and days 9 to 12, in Cycles 1 and 2, and on days 1 to 4 in Cycles 3 and 4). Autologous stem cell transplants

were received by 198 (82%) patients and 208 (87%) patients in the VDDx and BDx groups respectively; the majority of patients underwent one single transplant procedure. Patient demographic and baseline disease characteristics were similar between the treatment groups. Median age of the patients in the study was 57 years, 55% were male and 48% of patients had high-risk cytogenetics. The median duration of treatment was 13 weeks for the VDDx group and 11 weeks for the BDx group. The median number of cycles received for both groups was 4 cycles. The primary efficacy endpoint of the study was post-induction response rate (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the bortezomib combined with dexamethasone group. Secondary efficacy endpoints included post-transplant response rates (CR+nCR, CR+nCR+VGPR+PR), Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 12.

Table 12: Efficacy results from study IFM-2005-01

Endpoints	**BDx**	**VDDx**	**OR; 95% CI; P value[a]**
IFM-2005-01	N=240 (ITT population)	N=242 (ITT population)	
RR (Post-induction) *CR+nCR CR+nCR+VGPR+PR % (95% CI)	 14.6 (10.4, 19.7) 77.1 (71.2, 82.2)	 6.2 (3.5, 10.0) 60.7 (54.3, 66.9)	 2.58 (1.37, 4.85); 0.003 2.18 (1.46, 3.24); < 0.001
RR(Post-transplant)[b] CR+nCR CR+nCR+VGPR+PR % (95% CI)	 37.5 (31.4, 44.0) 79.6 (73.9, 84.5)	 23.1 (18.0, 29.0) 74.4 (68.4, 79.8)	 1.98 (1.33, 2.95); 0.001 1.34 (0.87, 2.05); 0.179

CI=confidence interval; CR=complete response; nCR=near complete response; ITT = intent to treat; RR= response rate; B= bortezomib; BDx= bortezomib, dexamethasone; VDDx=vincristine, doxorubicin, dexamethasone; VGPR=very good partial response; PR=partial response; OR=odds ratio.

* Primary endpoint

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.

[b] Refers to response rate after second transplant for subjects who received a second transplant (42/240 [18%] in BDx group and 52/242 [21%] in VDDx group).

Note: An OR > 1 indicates an advantage for B-containing induction therapy.

In study MMY-3010 induction treatment with bortezomib combined with thalidomide and dexamethasone [BTDx, n=130] was compared to thalidomide-dexamethasone [TDx, n=127]. Patients in the BTDx group received six 4-week cycles, each consisting of bortezomib (1.3 mg/m^2 administered twice weekly days 1, 4, 8, and 11, followed by a 17-day rest period from day 12 to day 28), dexamethasone (40 mg administered orally on days 1 to 4 and days 8 to 11), and thalidomide (administered orally at 50 mg daily on days 1-14, increased to 100 mg on days 15-28 and thereafter to 200 mg daily).

One single autologous stem cell transplant was received by 105 (81%) patients and 78 (61%) patients in the BTDx and TDx groups, respectively. Patient demographic and baseline disease characteristics were similar between the treatment groups. Patients in the BTDx and TDx groups respectively had a median age of 57 versus 56 years, 99% versus 98% patients were Caucasians, and 58% versus 54% were males. In the BTDx group 12% of patients were cytogenetically classified as high risk versus 16% of patients in the TDx group. The median duration of treatment was 24.0 weeks and the median number of treatment cycles received was 6.0, and was consistent

across treatment groups. The primary efficacy endpoints of the study were post-induction and post-transplant response rates (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the bortezomib combined with dexamethasone and thalidomide group. Secondary efficacy endpoints included Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 13.

Table 13: Efficacy results from study MMY-3010

Endpoints	**BTDx**	**TDx**	**OR; 95% CI; P value[a]**
MMY-3010	N=130 (ITT population)	N=127 (ITT population)	
**RR (Post-induction)* CR+nCR CR+nCR+PR % (95% CI)	 49.2 (40.4, 58.1) 84.6 (77.2, 90.3)	 17.3 (11.2, 25.0) 61.4 (52.4, 69.9)	 4.63 (2.61, 8.22); < 0.001[a] 3.46 (1.90, 6.27); < 0.001[a]
**RR (Post-transplant)* CR+nCR CR+nCR+PR % (95% CI)	 55.4 (46.4, 64.1) 77.7 (69.6, 84.5)	 34.6 (26.4, 43.6) 56.7 (47.6, 65.5)	 2.34 (1.42, 3.87); 0.001[a] 2.66 (1.55, 4.57); < 0.001[a]

CI=confidence interval; CR=complete response; nCR=near complete response; ITT = intent to treat; RR= response rate; B= bortezomib; BTDx= bortezomib, thalidomide, dexamethasone; TDx=thalidomide, dexamethasone ; PR=partial response; OR=odds ratio

* Primary endpoint

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.

Note: An OR > 1 indicates an advantage for B-containing induction therapy

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 III 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 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.

In the Phase III study, treatment with bortezomib led to a significantly longer time to progression, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone (see Table 14), in all patients as well as in patients who have received 1 prior line of therapy. 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 randomised to dexamethasone were then offered bortezomib, regardless of disease status. Due to this early crossover, the median duration of follow-up for surviving patients is 8.3 months. Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the bortezomib arm.

Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for bortezomib independently of age. Regardless of $ß_2$-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the bortezomib arm.

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

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

Table 14: 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, 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 (%)	**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]	56 (18)[b]	57 (45)[d]	29 (26)[d]	64 (34)[b]	27 (13)[b]	(27)**
CR+nCR+PR+M R	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 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 15).

Table 15: 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	8.0		10.2
(95% CI)	(6.7, 9.8)		(8.1, 10.8)
Hazard 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)	(64.1, 85.4)		(63.1, 80.0)

[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

Bortezomib combination treatment with pegylated liposomal doxorubicin (study DOXIL MMY-3001)

A Phase III randomised, parallel-group, open-label, multicentre study was conducted in 646 patients comparing the safety and efficacy of bortezomib plus pegylated liposomal doxorubicin versus bortezomib monotherapy in patients with multiple myeloma who had received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy. The primary efficacy endpoint was TTP while the secondary efficacy endpoints were OS and ORR (CR+PR), using the European Group for Blood and Marrow Transplantation (EBMT) criteria.

A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45 % (95 % CI; 29-57 %, $p < 0.0001$) for patients treated with combination therapy of bortezomib and pegylated liposomal doxorubicin. The median TTP was 6.5 months for the bortezomib monotherapy patients compared with 9.3 months for the bortezomib plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.

The final analysis for OS performed after a median follow-up of 8.6 years showed no significant difference in OS between the two treatment arms. The median OS was 30.8 months (95% CI; 25.2-36.5 months) for the bortezomib monotherapy patients and 33.0 months (95% CI; 28.9-37.1 months) for the bortezomib plus pegylated liposomal doxorubicin combination therapy patients.

Bortezomib combination treatment with dexamethasone

In the absence of any direct comparison between bortezomib and bortezomib in combination with dexamethasone in patients with progressive multiple myeloma, a statistical matched-pair analysis was conducted to compare results from the non randomised arm of bortezomib in combination with dexamethasone (Phase II open-label study MMY-2045), with results obtained in the bortezomib monotherapy arms from different Phase III randomised studies (M34101-039 [APEX] and DOXIL MMY-3001) in the same indication.

The matched-pair analysis is a statistical method in which patients in the treatment group (e.g. bortezomib in combination with dexamethasone) and patients in the comparison group (e.g. bortezomib) are made comparable with respect to confounding factors by individually pairing study subjects. This minimises the effects of observed confounders when estimating treatment effects using non-randomised data.

One hundred and twenty seven matched pairs of patients were identified. The analysis demonstrated improved ORR (CR+PR) (odds ratio 3.769; 95% CI 2.045-6.947; $p < 0.001$), PFS

(hazard ratio 0.511; 95% CI 0.309-0.845; p=0.008), TTP (hazard ratio 0.385; 95% CI 0.212-0.698; p=0.001) for bortezomib in combination with dexamethasone over bortezomib monotherapy.
Limited information on bortezomib retreatment in relapsed multiple myeloma is available.
Phase II study MMY-2036 (RETRIEVE), single arm, open-label study was conducted to determine the efficacy and safety of retreatment with bortezomib. One hundred and thirty patients (≥ 18 years of age) with multiple myeloma who previously had at least partial response on a bortezomib-containing regimen were retreated upon progression. At least 6 months after prior therapy, bortezomib was started at the last tolerated dose of 1.3 mg/m2 (n=93) or ≤ 1.0 mg/m2 (n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with bortezomib to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of bortezomib retreatment cycles. The primary endpoint was best confirmed response to retreatment as assessed by EBMT criteria. The overall best response rate (CR + PR), to retreatment in 130 patients was 38.5% (95% CI: 30.1, 47.4).
Clinical efficacy in previously untreated mantle cell lymphoma (MCL)
Study LYM-3002 was a Phase III, randomised, open-label study comparing the efficacy and safety of the combination of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the BR-CAP treatment arm received bortezomib (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day bortezomib treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given.
The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.
The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 76% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow-up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the BR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups completed treatment, 80% in the BR-CAP group and 82% in the R-CHOP group. Efficacy results are presented in Table 16:
Table 16: Efficacy results from study LYM-3002

Efficacy endpoint	**BR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7%)	165 (67.6%)	HR[b] (95% CI)=0.63 (0.50; 0.79) p-value[d]< 0.001
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Response rate			

n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[f] n(%)	122 (53.3%)	95 (41.7%)	OR[e] (95% CI)=1.688 (1.148; 2.481) p-value[g]=0.007
Overall response (CR+CRu+PR)[h] n(%)	211 (92.1%)	204 (89.5%)	OR[e] (95% CI)=1.428 (0.749; 2.722) p-value[g]=0.275

[a] Based on Independent Review Committee (IRC) assessment (radiological data only).
[b] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for BR-CAP.
[c] Based on Kaplan-Meier product limit estimates.
[d] Based on Log rank test stratified with IPI risk and stage of disease.
[e] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and stage of disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for BR-CAP.
[f]Include all CR+CRu, by IRC, bone marrow and LDH.
[g]P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.
[h]Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
CR=Complete Response; CRu=Complete Response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=Hazard Ratio; OR=Odds Ratio; ITT=Intent to Treat

Median PFS by investigator assessment was 30.7 months in the BR-CAP group and 16.1 months in the R-CHOP group (Hazard Ratio [HR]=0.51; p < 0.001). A statistically significant benefit (p < 0.001) in favour of the BR-CAP treatment group over the R-CHOP group was observed for TTP (median 30.5 versus 16.1 months), TNT (median 44.5 versus 24.8 months) and TFI (median 40.6 versus 20.5 months). The median duration of complete response was 42.1 months in the BR-CAP group compared with 18 months in the R-CHOP group. The duration of overall response was 21.4 months longer in the BR-CAP group (median 36.5 months versus 15.1 months in the R-CHOP group). The final analysis for OS was performed after a median follow-up of 82 months. Median OS was 90.7 months for the BR-CAP group compared with 55.7 months in the R-CHOP group (HR=0.66; p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

Patients with previously treated light-chain (AL) Amyloidosis

An open label non randomised Phase I/II study was conducted to determine the safety and efficacy of bortezomib in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular bortezomib did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis, a 67.3% response rate (including a 28.6% CR rate) as measured by hematologic response (M-protein) was reported in 49 evaluable patients treated with the maximum allowed doses of 1.6 mg/m2 weekly and 1.3 mg/m2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with bortezomib in all subsets of the paediatric population in multiple myeloma and in mantle cell lymphoma (see section 4.2 for information on paediatric use).

A Phase II, single-arm activity, safety, and pharmacokinetic trial conducted by the Children's Oncology Group assessed the activity of the addition of bortezomib to multi-agent re-induction chemotherapy in paediatric and young adult patients with lymphoid malignancies (pre-B cell

acute lymphoblastic leukemia [ALL], T-cell ALL, and T-cell lymphoblastic lymphoma [LL]). An effective re-induction multi-agent chemotherapy regimen was administered in 3 blocks. Bortezomib was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with co-administered drugs in Block 3.
Complete response (CR) was evaluated at the end of Block 1. In B-ALL patients with relapse within 18 months of diagnosis (n = 27) the CR rate was 67% (95% CI: 46, 84); the 4-month event free survival rate was 44% (95% CI: 26, 62). In B-ALL patients with relapse 18-36 months from diagnosis (n = 33) the CR rate was 79% (95% CI: 61, 91) and the 4-month event free survival rate was 73% (95% CI: 54, 85). The CR rate in first-relapsed T-cell ALL patients (n = 22) was 68% (95% CI: 45, 86) and the 4-month event free survival rate was 67% (95% CI: 42, 83). The reported efficacy data are considered inconclusive (see section 4.2).
There were 140 patients with ALL or LL enrolled and evaluated for safety; median age was 10 years (range 1 to 26). No new safety concerns were observed when bortezomib was added to the standard pediatric pre-B cell ALL chemotherapy backbone. The following adverse reactions (Grade ≥ 3) were observed at a higher incidence in the bortezomib containing treatment regimen as compared with a historical control study in which the backbone regimen was given alone: in Block 1 peripheral sensory neuropathy (3% versus 0%); ileus (2.1% versus 0%); hypoxia (8% versus 2%). No information on possible sequelae or rates of peripheral neuropathy resolution were available in this study. Higher incidences were also noted for infections with Grade ≥ 3 neutropenia (24% versus 19% in Block 1 and 22% versus 11% in Block 2), increased ALT (17% versus 8% in Block 2), hypokalaemia (18% versus 6% in Block 1 and 21% versus 12% in Block 2) and hyponatraemia (12% versus 5% in Block 1 and 4% versus 0 in Block 2).

5.2 Pharmacokinetic properties

Absorption
Following intravenous bolus administration of a 1.0 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 to 106 ng/ml for the 1.0 mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose.
Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients with multiple myeloma (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%-122.80%.
Distribution
The mean distribution volume (V_d) of bortezomib ranged from 1,659 l to 3,294 l following single- or repeated-dose intravenous administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. Over a bortezomib concentration range of 0.01 to 1.0 µg/ml, the *in vitro* protein binding averaged 82.9% in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.
Biotransformation
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450

enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Special populations

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib 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 6).

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/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

Age

The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to 104 pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2, volume of distribution at steady-state was 834 (39%) L/m^2, and the elimination half-life was 100 (44%) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

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-foetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lymphoid tissue atrophy and 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/m2 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 & 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

Unopened vial

2 years

Reconstituted solution

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, the storage times and conditions during use, prior to administration, are the responsibility of the user. However, the reconstituted solution is stable for 8 hours at 25 ° C, stored in the original vial and / or syringe, where the total storage time for the reconstituted medicine should not exceed 8 hours before administration.
BORTEZOMIB NEAPOLIS is for single use only. Any unused medicine or waste must be disposed of in accordance with local requirements.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not store above 30 ° C
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

BORTEZOMIB NEAPOLISis packed in a colorless type I glass 10 ml vial.

6.6 Special precautions for disposal and other handling

General precautions

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

Pregnant personnel should not handle this medicine.

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

Instructions for reconstitution

BORTEZOMIB NEAPOLIS must be reconstituted by a healthcare professional.

Intravenous injection

I. RECONSTITUTION FOR INTRAVENOUS ADMINISTRATION

Note: BORTEZOMIB NEAPOLIS is a cytotoxic agent. Therefore, caution is recommended during handling and preparation. The use of gloves and other protective material is recommended to avoid contact with the skin.

THE ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED DURING THE HANDLING OF BORTEZOMIB NEAPOLIS AS IT DOES NOT CONTAIN ANY CONSERVATIVE.

Preparation of the 3.5 mg vial: carefully add 3.5 ml of sterile sodium chloride 9 mg / ml (0.9%) solution for injections to the vial containing the BORTEZOMIB NEAPOLIS powder, using a syringe of the appropriate volume without removing the cap. Dissolving the lyophilized powder is complete in less than 2 minutes.
The concentration of the final solution will be 1 mg / ml. The solution will be clear and colorless, with a final pH of 4 to 7. It is not necessary to check the final pH.

Before administration, visually inspect for particulate matter and discoloration. If any discoloration or the presence of particles is observed, the solution should be discarded. Confirm the concentration in the vial to ensure that the correct dose is being administered intravenously (1 mg / ml).

The reconstituted solution does not contain preservatives and should be used immediately after preparation. The chemical and physical stability of the reconstituted solution has been demonstrated for a total of 8 hours at 25 ° C in the original vial and / or syringe. The total storage time for the reconstituted solution should not exceed 8 hours before administration. If the reconstituted solution is not used immediately, the time it is stored and the conditions of storage before use are the responsibility of the user.
It is not necessary to protect the reconstituted medicine from light.

II. ADMINISTRATION

• Once dissolved, withdraw the appropriate amount of reconstituted solution according to the calculated dose and based on the patient's Body Surface Area.
• Confirm the dose and concentration in the syringe before use (check that the syringe is marked for intravenous administration).
• Inject the solution into the vein in a 3-5 second bolus intravenous through a peripheral or central intravenous catheter.
• Wash the intravenous or peripheral catheter with a sterile sodium chloride 9 mg / ml (0.9%) solution for injections.
BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection MUST BE ADMINISTERED INTRAVENOUS OR SUBCUTANEOUS.
Do not use in other ways. Intrathecal administration resulted in death.

III. DISPOSAL

A vial is for single use and the unused solution must be discarded.
Unused products or waste must be disposed of in accordance with local requirements.

The following information is intended for healthcare professionals only:
As described below, only the 3.5 mg vial can be administered subcutaneously.

Subcutaneous injection

I. RECONSTITUTION FOR SUBCUTANEOUS ADMINISTRATION

Note: BORTEZOMIB NEAPOLIS is a cytotoxic agent. Therefore, caution is recommended during handling and preparation. The use of gloves and other protective material is recommended to avoid skin contact.
THE ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED DURING THE HANDLING OF BORTEZOMIB NEAPOLIS AS IT DOES NOT CONTAIN ANY CONSERVATIVE.
Preparation of the 3.5 mg vial: carefully add 1.4 ml of sterile sodium chloride 9 mg / ml (0.9%) solution for injections to the vial containing the BORTEZOMIB NEAPOLIS powder, using a syringe of the appropriate volume without removing the cap. Dissolving the lyophilized powder is complete in less than 2 minutes.
The concentration of the final solution will be 2.5 mg / ml. The solution will be clear and colorless, with a final pH of 4 to 7. It is not necessary to check the final pH.

Before administration, visually inspect for particulate matter and discoloration. If any discoloration or the presence of particles is observed, the solution should be discarded. Make sure that the correct dose is being administered subcutaneously (2.5 mg / ml).

The reconstituted solution does not contain preservatives and should be used immediately after preparation. The chemical and physical stability of the reconstituted solution has been demonstrated for a total of 8 hours at 25 ° C in the original vial and / or syringe. The total storage time for the reconstituted solution should not exceed 8 hours before administration. If the reconstituted solution is not used immediately, the time it is stored and the conditions of storage before use are the responsibility of the user.
It is not necessary to protect the reconstituted medicine from light.

II. ADMINISTRATION

• Once dissolved, withdraw the appropriate amount of reconstituted solution according to the calculated dose and based on the patient's Body Surface Area.
• Confirm the dose and concentration in the syringe before use (check that the syringe is marked for subcutaneous administration).
• Inject the solution subcutaneously, at an angle of 45-90 °.
• The reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left).
• The injection sites for successive injections must be rotary.
• If reactions occur at the injection sites after subcutaneous injection of BORTEZOMIB NEAPOLIS, it is recommended to administer a less concentrated BORTEZOMIB NEAPOLIS solution (1 mg / ml instead of 2.5 mg / ml) or switch to an intravenous injection.
BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection MUST BE ADMINISTERED INTRAVENOUS OR SUBCUTANEOUS. Do not use in other ways. Intrathecal administration resulted in death.

III. DISPOSAL

A vial is for single use and the unused solution must be discarded.
Unused products or waste must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection:9393051H.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/02/2019.

10. DATE OF REVISION OF THE TEXT

12/2019.