ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib Fresenius Kabi 1 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg bortezomib (as a mannitol boronic ester).

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.

White to off-white lyophilized powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bortezomib 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 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 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 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

Bortezomib treatment must be initiated under supervision of a physician experienced in the treatment of cancer patients, however bortezomib 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).

<u>Posology for treatment of progressive multiple myeloma (patients who have received at least one prior therapy)</u>
Monotherapy
Bortezomib Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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.

Pegylated liposomal doxorubicin is administered at 30 mg/m^2 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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	Day 1, 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=bortezomib; 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 Fresenius Kabi 1 mg powder for solution for injection is administered via intravenous 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-1.5 x ULN	Any	None
Moderate	> 1.5 x-3 x 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 Fresenius Kabi 1 mg powder for solution for injection is available for intravenous administration only.

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

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

Intravenous injection
Bortezomib Fresenius Kabi 1 mg powder for solution for injection is for intravenous administration only. The reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. At least 72 hours should elapse between consecutive doses of bortezomib.

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

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 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 Fresenius Kabi 1 mg powder for solution for injection is for intravenous use only, while Bortezomib Fresenius Kabi 2.5 and 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib 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 $< 75,000/\mu l$, 90% of 21 patients had a count $\leq 25,000/\mu l$ during the study, including 14% $< 10,000/\mu l$; in contrast, with a baseline platelet count $> 75,000/\mu l$, only 14% of 309 patients had a count $\leq 25,000/\mu l$ 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.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose or schedule of bortezomib (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% ($CI_{90\%}$ [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (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 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of bortezomib (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with bortezomib and for 8 months following completion of treatment. Male patients should use effective contraceptive measures and be advised not to father a child while receiving bortezomib and for 5 months following completion of treatment (see section 5.3).

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). Due to the genotoxic potential of bortezomib (see section 5.3), male patients should seek advice on conservation of sperm and women of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment.

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 list 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, Thrombotic microangiopathy (including thrombocytopenic purpura)[#], Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
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

System Organ Class	Incidence	Adverse reaction
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, Guillain-Barré syndrome [#], Demyelinating polyneuropathy [#]
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion[#], Blepharitis[#], Eye inflammation*, 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

System Organ Class	Incidence	Adverse reaction
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

System Organ Class	Incidence	Adverse reaction
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

System Organ Class	Incidence	Adverse reaction
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
Renal and urinary disorders	Common	Renal impairment*
	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*

System Organ Class	Incidence	Adverse reaction
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.
# Postmarketing 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/m^2 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, anemia, 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 (≥ 1/1000 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

System Organ Class	Incidence	Adverse 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*
Nervous system disorders	Very common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	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*

System Organ Class	Incidence	Adverse reaction
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 (N=239)	BDx (N=239)	TDx (N=126)	BTDx (N=130)
Incidence of PN (%)				
All Grade PN	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 (BR-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 (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All Grade PN	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.

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 reporting system listed in Appendix V.

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: L01XG01.

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 hemoglobin of 105 g/l, and a median platelet count of 221.5 x 10^9/l. Similar proportions of patients had creatinine clearance ≤ 30 ml/min (3% in each arm).

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the 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+PR[f]	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:

β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR+PR) from the Cochran Mantel-Haenszel 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 charateristics 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	49.2 (40.4, 58.1)	17.3 (11.2, 25.0)	4.63 (2.61, 8.22); < 0.001[a]
CR+nCR+PR % (95% CI)	84.6 (77.2, 90.3)	61.4 (52.4, 69.9)	3.46 (1.90, 6.27); < 0.001[a]
**RR (Post-transplant)*			
CR+nCR	55.4 (46.4, 64.1)	34.6 (26.4, 43.6)	2.34 (1.42, 3.87); 0.001[a]
CR+nCR+PR % (95% CI)	77.7 (69.6, 84.5)	56.7 (47.6, 65.5)	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; 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 bortezomib-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 β_2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the bortezomib arm.

In the refractory population of the Phase II study, responses were determined by an independent review committee and the response criteria were those of the European Bone Marrow Transplant Group. The median survival of all patients enrolled was 17 months (range < 1 to 36+ months). This survival was greater than the six-to-nine month median survival anticipated by consultant clinical investigators for a similar patient population. By multivariate analysis, the response rate was independent of myeloma type, performance status, chromosome 13 deletion status, or the number or type of previous therapies. Patients who had received 2 to 3 prior therapeutic regimens had a response rate of 32% (10/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67).

Table 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+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	63 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	126 (4.1)	385*
Time to response CR+PR (days)	43	43	44	46	41	27	38*

[a] Intent to Treat (ITT) population
[b] p-value from the stratified log-rank test; analysis by line of therapy excludes stratification for therapeutic history; $p < 0.0001$
[c] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study 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.

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/m^2 (n=93) or ≤ 1.0 mg/m^2 (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 15:

Table 15: 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 for 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/m^2 weekly and 1.3 mg/m^2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with bortezomib in all subsets of the paediatric population in multiple myeloma 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 reinduction multiagent chemotherapy regimen was administered in 3 blocks. Bortezomib was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with coadministered 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.

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 showed genotoxic potential. 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 positive when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed 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/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)

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 chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage condition.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml clear Type I glass vial with grey chlorobutyl rubber stopper and green aluminium flip-off over seal, containing 1 mg bortezomib.

The vial is shrink wrapped (without tray) or placed in a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

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

Aseptic technique must be strictly observed throughout the handling of bortezomib, since it contains no preservative.
There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib Fresenius Kabi 1 mg powder for solution for injection is for intravenous use only, while Bortezomib Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.

Instructions for reconstitution
Bortezomib must be reconstituted by a healthcare professional.

Each 5 ml vial of Bortezomib Fresenius Kabi 1 mg powder for solution for injection must be carefully reconstituted with 1 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1397/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2019

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of European Medicinal Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Each vial contains 2.5 mg bortezomib (as a mannitol boronic ester).

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

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.

White to off-white lyophilized powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bortezomib 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 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 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 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

Bortezomib treatment must be initiated under supervision of a physician experienced in the treatment of cancer patients, however bortezomib 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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.

Pegylated liposomal doxorubicin is administered at 30 mg/m^2 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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 $\geq 70 \times 10^9$/l and the absolute neutrophils count should be $\geq 1.0 \times 10^9$/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 $\leq 30 \times 10^9$/l or ANC $\leq 0.75 \times 10^9$/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.

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

Combination therapy with dexamethasone

Bortezomib Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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	Day 1, 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=bortezomib; 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 Fresenius Kabi 2.5 mg and 3.5 mg powder for solution for injection 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-1.5 x ULN	Any	None
Moderate	> 1.5 x-3 x 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 Fresenius Kabi 1 mg powder for solution for injection is available for intravenous administration only.

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

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

Intravenous injection
Bortezomib 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 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 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.

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 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 Fresenius Kabi 1 mg powder for solution for injection is for intravenous use only, while Bortezomib Fresenius Kabi 2.5 and 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib 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, schedule 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% ($CI_{90\%}$ [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (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 Fertility, pregnancy and lactation

Contraception in males and females
Due to the genotoxic potential of bortezomib (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with bortezomib and for 8 months following treatment. Male patients should use effective contraceptive measures and be advised not to father a child while receiving bortezomib and for 5 months following completion of treatment (see section 5.3).

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). Due to the genotoxic potential of bortezomib (see section 5.3), male patients should seek advice on conservation of sperm and women of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment.

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 list 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, Thrombotic microangiopathy (including thrombocytopenic purpura)[#], Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
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

System Organ Class	Incidence	Adverse reaction
	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, Guillain-Barré syndrome [#], Demyelinating polyneuropathy [#]

System Organ Class	Incidence	Adverse reaction
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion[#], Blepharitis[#], Eye inflammation*, 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

System Organ Class	Incidence	Adverse reaction
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

System Organ Class	Incidence	Adverse reaction
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
Renal and urinary disorders	Common	Renal impairment*
	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

System Organ Class	Incidence	Adverse reaction
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.
# Postmarketing 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/m^2 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, anemia, 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*
Nervous system disorders	Very common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	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)

System Organ Class	Incidence	Adverse reaction
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 (N=239)	BDx (N=239)	TDx (N=126)	BTDx (N=130)
Incidence of PN (%)				
All Grade PN	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 (BR-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 (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All Grade PN	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 reporting system listed in Appendix V.

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: L01XG01.

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 hemoglobin of 105 g/l, and a median platelet count of 221.5 x 10^9/l. Similar proportions of patients had creatinine clearance ≤ 30 ml/min (3% in each arm).

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the 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	

Efficacy endpoint	**B+M+P n=344**	**M+P n=338**
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+PR[f]	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: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR+PR) from the Cochran Mantel-Haenszel 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 charateristics 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	49.2 (40.4, 58.1)	17.3 (11.2, 25.0)	4.63 (2.61, 8.22); < 0.001[a]
CR+nCR+PR % (95% CI)	84.6 (77.2, 90.3)	61.4 (52.4, 69.9)	3.46 (1.90, 6.27); < 0.001[a]
**RR (Post-transplant)* CR+nCR	55.4 (46.4, 64.1)	34.6 (26.4, 43.6)	2.34 (1.42, 3.87); 0.001[a]
CR+nCR+PR % (95% CI)	77.7 (69.6, 84.5)	56.7 (47.6, 65.5)	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; 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 bortezomib-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 β_2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the bortezomib arm.

In the refractory population of the Phase II study, responses were determined by an independent review committee and the response criteria were those of the European Bone Marrow Transplant Group. The median survival of all patients enrolled was 17 months (range < 1 to 36+ months). This survival was greater than the six-to-nine month median survival anticipated by consultant clinical investigators for a similar patient population. By multivariate analysis, the response rate was independent of myeloma type, performance status, chromosome 13 deletion status, or the number or type of previous therapies. Patients who had received 2 to 3 prior therapeutic regimens had a

response rate of 32% (10/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67).

Table 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+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	63 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	126 (4.1)	385*
Time to response CR+PR (days)	43	43	44	46	41	27	38*

[a] Intent to Treat (ITT) population
[b] p-value from the stratified log-rank test; analysis by line of therapy excludes stratification for therapeutic history; $p < 0.0001$
[c] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study 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/m^2 (n=93) or ≤ 1.0 mg/m^2 (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).

<u>Clinical efficacy in previously untreated mantle cell lymphoma (MCL)</u>
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 for 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/m^2 weekly and 1.3 mg/m^2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with bortezomib in all subsets of the paediatric population in multiple myeloma 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 reinduction multiagent chemotherapy regimen was administered in 3 blocks. Bortezomib was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with coadministered 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 $\geq$ 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 showed genotoxic potential. 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 positive when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed 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/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)

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 chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml and 2.5 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8 °C) prior to administration.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage condition.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
10 ml clear Type I glass vial with grey chlorobutyl rubber stopper and yellow aluminium flip-off over seal, containing 2.5 mg bortezomib.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
10 ml clear Type I glass vial with grey chlorobutyl rubber stopper and blue aluminium flip-off over seal, containing 3.5 mg bortezomib.

The vial is shrink wrapped (without tray) or placed in a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

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

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

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib Fresenius Kabi 1 mg powder for solution for injection is for intravenous use only, while Bortezomib Fresenius Kabi 2.5 and 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.

Instructions for reconstitution
Bortezomib must be reconstituted by a healthcare professional.

Intravenous injection
Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Each 10 ml vial of Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection must be carefully reconstituted with 2.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
Each 10 ml vial of Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

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

Subcutaneous injection
Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Each 10 ml vial of Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection must be carefully reconstituted with 1 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
Each 10 ml vial of bortezomib must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1397/003
EU/1/19/1397/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2019

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of European Medicinal Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg,
Germany

or
Fresenius Kabi Polska Sp. z.o.o.,
ul. Sienkiewicza 25, Kutno,
99-300, Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib Fresenius Kabi 1 mg powder for solution for injection
bortezomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg bortezomib (as a mannitol boronic ester).

3. LIST OF EXCIPIENTS

Mannitol (E421)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.
For single use.
May be fatal if given by other routes.
Intravenous use: Add 1 ml sodium chloride 0.9% to make 1 mg/ml final concentration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic
Handle with care

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10, SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1397/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bortezomib Fresenius Kabi 1 mg powder for solution for injection
bortezomib
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

Cytotoxic
May be fatal if given by other routes

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
bortezomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2.5 mg bortezomib (as a mannitol boronic ester).

3. LIST OF EXCIPIENTS

Mannitol (E421)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous or intravenous use after reconstitution
For single use.
May be fatal if given by other routes.
Subcutaneous use: Add 1 ml sodium chloride 0.9% to make 2.5 mg/ml final concentration.
Intravenous use: Add 2.5 ml sodium chloride 0.9% to make 1 mg/ml final concentration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic
Handle with care

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1397/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
bortezomib
SC or IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mg

6. OTHER

Cytotoxic
May be fatal if given by other routes

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
bortezomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

3. LIST OF EXCIPIENTS

Mannitol (E421)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous or intravenous use after reconstitution
For single use.
May be fatal if given by other routes.
Subcutaneous use: Add 1.4 ml sodium chloride 0.9% to make 2.5 mg/ml final concentration.
Intravenous use: Add 3.5 ml sodium chloride 0.9% to make 1 mg/ml final concentration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic
Handle with care

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1397/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
bortezomib
SC or IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.5 mg

6. OTHER

Cytotoxic
May be fatal if given by other routes

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bortezomib Fresenius Kabi 1 mg powder for solution for injection
bortezomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Bortezomib Fresenius Kabi is and what it is used for

This medicine contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

Bortezomib is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Bortezomib is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use Bortezomib Fresenius Kabi

Do not use bortezomib
- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine (listed in section 6)
- if you have certain severe lung or heart problems.

Warnings and precautions
You must tell your doctor if you have any of the following:

- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood
- diarrhoea, constipation, nausea or vomiting
- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with bortezomib, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with bortezomib you must tell your doctor:
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with bortezomib for information related to these medicines before starting treatment with bortezomib. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents
This medicine must not be used in children and adolescents because it is not known how it will affect them.

Other medicines and bortezomib
Please tell your doctor, or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are using medicines containing any of the following active substances:
- ketoconazole, used to treat fungal infections
- ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John’s Wort (Hypericum perforatum), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding
You must not use this medicine if you are pregnant, unless clearly necessary.

Women of childbearing potential must use effective contraception during treatment and for 8 months following completion of treatment. Talk to your doctor if you wish to freeze your eggs before starting treatment.
Men should not father a child while using bortezomib and should use effective contraception during treatment and for up to 5 months after treatment has stopped. Talk to your doctor if you wish to

conserve your sperm before starting treatment.

You must not breast-feed while using bortezomib. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and foetal death. When bortezomib is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines
Bortezomib might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you must still be cautious.

3. How to use Bortezomib Fresenius Kabi

Your doctor will work out your dose of bortezomib according to your height and weight (body surface area). The usual starting dose of bortezomib is 1.3 mg/m^2 body surface area twice a week. Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When bortezomib is given alone, you will receive 4 doses of bortezomib intravenously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given bortezomib together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When bortezomib is given together with pegylated liposomal doxorubicin, you will receive bortezomib intravenously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the bortezomib 21-day treatment cycle as an intravenous infusion after the bortezomib injection.
You might receive up to 8 cycles (24 weeks).

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of the bortezomib, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma
If you have not been treated before for multiple myeloma, and you are not suitable for blood stem cell transplantation you will receive bortezomib intravenously together with two other medicines; melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).

- In cycles 1 to 4, bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, bortezomib is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle.

If you have not been treated before for multiple myeloma, and you are suitable for blood stem cell transplantation you will receive bortezomib intravenously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib 21-day treatment cycle.
You will receive 4 cycles (12 weeks).

When bortezomib is given together with thalidomide and dexamethasone, the duration of a treatment cycle is 28 days (4 weeks).

Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards.
You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma
If you have not been treated before for mantle cell lymphoma you will receive bortezomib intravenously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.
Bortezomib is given intravenously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each bortezomib 21-day 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 given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the bortezomib treatment cycle.

How bortezomib is given
This medicine is for intravenous use only. Bortezomib will be administered by a health care professional experienced in the use of cytotoxic medicines.
Bortezomib powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then injected into a vein rapidly, over 3 to 5 seconds.

If you are given too much bortezomib
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much.
In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.
If you are given bortezomib for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with bortezomib can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with bortezomib, to check your blood cell counts regularly. You may experience a reduction in the number of:
- platelets, which may make you be more prone to bruising, or to bleeding without obvious

injury (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms.

If you are given bortezomib for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Reduction in the number of red blood cells and or white blood cells (see above)
- Fever
- Feeling sick (nausea) or vomiting, loss of appetite
- Constipation with or without bloating (can be severe)
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you another medicine to control diarrhoea
- Tiredness (fatigue), feeling weak
- Muscle pain, bone pain

Common side effects (may affect up to 1 in 10 people)
- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- Shivering
- Infections, including pneumonia, respiratory infections, bronchitis, fungal infections, coughing with phlegm, flu like illness
- Shingles (localised including around the eyes or spread across the body)
- Chest pains or shortness of breath with exercise
- Different types of rash
- Itching of the skin, lumps on the skin or dry skin
- Facial blushing or tiny broken capillaries
- Redness of the skin
- Dehydration
- Heartburn, bloating, belching, wind, stomach pain, bleeding from your bowels or stomach
- Alteration of liver functioning
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle spasms, muscle weakness, pain in your limbs
- Blurred vision
- Infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Nose bleeds
- Difficulty or problems in sleeping, sweating, anxiety, mood swings, depressed mood, restlessness or agitation, changes in your mental status, disorientation
- Swelling of body, to include around eyes and other parts of the body

Uncommon side effects (may affect up to 1 in 100 people)
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Inflammation of a vein, blood clots in your veins and lungs

- Problems with blood clotting
- Insufficient circulation
- Inflammation of the lining around your heart or fluid around your heart
- Infections including urinary tract infections, the flu, herpes virus infections, ear infection and cellulitis
- Bloody stools, or bleeding from mucosal membranes, e.g., mouth, vagina
- Cerebrovascular disorders
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching
- Arthritis, including inflammation of the joints in the fingers, toes, and the jaw
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Hiccups, speech disorders
- Increased or decreased urine production (due to kidney damage), painful passing of urine or blood/proteins in the urine, fluid retention
- Altered levels of consciousness, confusion, memory impairment or loss
- Hypersensitivity
- Hearing loss, deafness or ringing in the ears, ear discomfort
- Hormone abnormality which may affect salt and water absorption
- Overactive thyroid gland
- Inability to produce enough insulin or resistance to normal levels of insulin
- Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion), red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions
- Redness or pain at the injection site
- Mouth pain
- Infections or inflammation of the mouth, mouth ulcers, oesophagus, stomach and intestines, sometimes associated with pain or bleeding, poor movement of the intestines (including blockage), abdominal or oesophageal discomfort, difficulty swallowing, vomiting of blood
- Skin infections
- Bacterial and viral infections
- Tooth infection
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Inflammation or haemorrhage of the blood vessels that can appear as small red or purple dots (usually on the legs) to large bruise-like patches under the skin or tissue
- Benign cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.

Rare side effects (may affect up to 1 in 1,000 people)

- Heart problems to include heart attack, angina

- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)

- Flushing
- Discoloration of the veins
- Inflammation of the spinal nerve
- Problems with your ear, bleeding from your ear
- Underactivity of your thyroid gland
- Budd–Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins)
- Changes in or abnormal bowel function
- Bleeding in the brain
- Yellow discolouration of eyes and skin (jaundice)
- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears
- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula
- Joint effusion
- Cysts in the lining of joints (synovial cysts)
- Fracture
- Breakdown of muscle fibers leading to other complications
- Swelling of the liver, bleeding from the liver
- Cancer of the kidney
- Psoriasis like skin condition
- Cancer of the skin
- Paleness of the skin
- Increase of platelets or plasma cells (a type of white cell) in the blood
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Abnormal reaction to blood transfusions
- Partial or total loss of vision
- Decreased sex drive
- Drooling
- Bulging eyes
- Sensitivity to light
- Rapid breathing
- Rectal pain
- Gallstones
- Hernia
- Injuries
- Brittle or weak nails
- Abnormal protein deposits in your vital organs
- Coma
- Intestinal ulcers
- Multi-organ failure
- Death

If you are given bortezomib together with other medicines for the treatment of mantle cell

lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)

- Pneumonia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Mouth ulcers
- Constipation
- Muscle pain, bone pain
- Hair loss and abnormal hair texture
- Tiredness, feeling weak
- Fever

Common side effects (may affect up to 1 in 10 people)

- Shingles (localized including around the eyes or spread across the body)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- Hypersensitivity (allergic reaction)
- Inability to produce enough insulin or resistance to normal levels of insulin
- Fluid retention
- Difficulty or problems in sleeping
- Loss of consciousness
- Altered level of consciousness, confusion
- Feeling dizzy
- Increased heartbeat, high blood pressure, sweating,
- Abnormal vision, blurred vision
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath with exercise
- Cough
- Hiccups
- Ringing in the ears, ear discomfort
- Bleeding from your bowels or stomach
- Heartburn
- Stomach pain, bloating
- Difficulty swallowing
- Infection or inflammation of the stomach and intestine
- Stomach pain
- Sore mouth or lip, throat pain
- Alteration of liver function
- Itching of skin
- Redness of skin
- Rash
- Muscle spasms
- Infection of the urinary tract
- Pain in limbs
- Swelling of body, to include eyes and other parts of the body

- Shivering
- Redness and pain at injection site
- General ill feeling
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)
- Hepatitis
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Movement disorders, paralysis, twitching
- Vertigo
- Hearing loss, deafness
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Blood clots in your lungs
- Yellow discoloration of the eyes and skin (jaundice)
- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bortezomib Fresenius Kabi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP.

This medicinal product does not require any special temperature storage condition. Keep the vial in the outer carton in order to protect from light.

The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration. Bortezomib is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Bortezomib Fresenius Kabi contains

- The active substance is bortezomib. Each vial contains 1 mg bortezomib (as a mannitol boronic ester). After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.
- The other ingredients are mannitol (E421).

What Bortezomib Fresenius Kabi looks like and contents of the pack
Bortezomib powder for solution for injection is a white to off-white lyophilized powder or cake.

Each carton of Bortezomib Fresenius Kabi 1 mg powder for solution for injection contains a 5 ml clear glass vial with grey rubber stopper and aluminium green flip-off over seal, containing 1 mg bortezomib.

The vial is shrink wrapped (without tray) or placed in a tray with a lid. Each pack contains 1 single-use vial.

Marketing Authorisation Holder
Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

Manufacturer
Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg,
Germany

or
Fresenius Kabi Polska Sp. z.o.o.,
ul. Sienkiewicza 25, Kutno,
99-300, Poland

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY

Other sources of information
Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

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

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

1.1 Preparation of the 1 mg vial: carefully add 1 ml of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the bortezomib by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution must be discarded Confirm concentration on vial to ensure that the correct dose is being given for the intravenous route of administration (1 mg/ml).

1.3 The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration.

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

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, sodium chloride 9 mg/ml (0.9%) solution.

Bortezomib Fresenius Kabi 1 mg IS FOR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material must be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
bortezomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Bortezomib Fresenius Kabi is and what it is used for

This medicine contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

Bortezomib is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Bortezomib is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use Bortezomib Fresenius Kabi

Do not use bortezomib
- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine (listed in section 6)
- if you have certain severe lung or heart problems.

Warnings and precautions
You must tell your doctor if you have any of the following:

- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood
- diarrhoea, constipation, nausea or vomiting
- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with bortezomib, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with bortezomib you must tell your doctor:
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with bortezomib for information related to these medicines before starting treatment with bortezomib. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents
This medicine must not be used in children and adolescents because it is not known how it will affect them.

Other medicines and bortezomib
Please tell your doctor, or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are using medicines containing any of the following active substances:
- ketoconazole, used to treat fungal infections
- ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John’s Wort (Hypericum perforatum), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding
You must not use this medicine if you are pregnant, unless clearly necessary.

Women of childbearing potential must use effective contraception during treatment and for 8 months following completion of treatment. Talk to your doctor if you wish to freeze your eggs before starting treatment.
Men should not father a child while using bortezomib and should use effective contraception during treatment and for up to 5 months after treatment has stopped. Talk to your doctor if you wish to

conserve your sperm before starting treatment.

You must not breast-feed while using bortezomib. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.
Thalidomide causes birth defects and foetal death. When bortezomib is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines
Bortezomib might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you must still be cautious.

3. How to use Bortezomib Fresenius Kabi

Your doctor will work out your dose of bortezomib according to your height and weight (body surface area). The usual starting dose of bortezomib is 1.3 mg/m^2 body surface area twice a week. Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When bortezomib is given alone, you will receive 4 doses of bortezomib intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given bortezomib together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When bortezomib is given together with pegylated liposomal doxorubicin, you will receive bortezomib intravenously or subcutaneously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the bortezomib 21-day treatment cycle as an intravenous infusion after the bortezomib injection.
You might receive up to 8 cycles (24 weeks).

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of the bortezomib, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma
If you have not been treated before for multiple myeloma, and you are not suitable for blood stem cell transplantation you will receive bortezomib together with two other medicines; melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).

- In cycles 1 to 4, bortezomib is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, bortezomib is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle.

If you have not been treated before for multiple myeloma, and you are suitable for blood stem cell transplantation you will receive bortezomib intravenously or subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib 21-day treatment cycle.
You will receive 4 cycles (12 weeks).

When bortezomib is given together with thalidomide and dexamethasone, the duration of a treatment cycle is 28 days (4 weeks).

Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the bortezomib 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards.
You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma
If you have not been treated before for mantle cell lymphoma you will receive bortezomib intravenously or subcutaneously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.
Bortezomib is given intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each bortezomib 21-day 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 given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the bortezomib treatment cycle.

How bortezomib is given
This medicine is for intravenous or subcutaneous use. Bortezomib will be administered by a health care professional experienced in the use of cytotoxic medicines.
Bortezomib powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then either injected into a vein or under the skin. Injection into a vein is rapid, taking 3 to 5 seconds. Injection under the skin is in either the thighs or the abdomen.

If you are given too much bortezomib
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much.
In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.
If you are given bortezomib for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with bortezomib can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with bortezomib, to check your blood cell counts regularly. You may

experience a reduction in the number of:

- platelets, which may make you be more prone to bruising, or to bleeding without obvious injury
  (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms.

If you are given bortezomib for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)

- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Reduction in the number of red blood cells and or white blood cells (see above)
- Fever
- Feeling sick (nausea) or vomiting, loss of appetite
- Constipation with or without bloating (can be severe)
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you another medicine to control diarrhoea
- Tiredness (fatigue), feeling weak
- Muscle pain, bone pain

Common side effects (may affect up to 1 in 10 people)

- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- Shivering
- Infections, including pneumonia, respiratory infections, bronchitis, fungal infections, coughing with phlegm, flu like illness
- Shingles (localised including around the eyes or spread across the body)
- Chest pains or shortness of breath with exercise
- Different types of rash
- Itching of the skin, lumps on the skin or dry skin
- Facial blushing or tiny broken capillaries
- Redness of the skin
- Dehydration
- Heartburn, bloating, belching, wind, stomach pain, bleeding from your bowels or stomach
- Alteration of liver functioning
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle spasms, muscle weakness, pain in your limbs
- Blurred vision
- Infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Nose bleeds
- Difficulty or problems in sleeping, sweating, anxiety, mood swings, depressed mood, restlessness or agitation, changes in your mental status, disorientation
- Swelling of body, to include around eyes and other parts of the body

Uncommon side effects (may affect up to 1 in 100 people)

- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Inflammation of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- Insufficient circulation
- Inflammation of the lining around your heart or fluid around your heart
- Infections including urinary tract infections, the flu, herpes virus infections, ear infection and cellulitis
- Bloody stools, or bleeding from mucosal membranes, e.g., mouth, vagina
- Cerebrovascular disorders
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching
- Arthritis, including inflammation of the joints in the fingers, toes, and the jaw
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Hiccups, speech disorders
- Increased or decreased urine production (due to kidney damage), painful passing of urine or blood/proteins in the urine, fluid retention
- Altered levels of consciousness, confusion, memory impairment or loss
- Hypersensitivity
- Hearing loss, deafness or ringing in the ears, ear discomfort
- Hormone abnormality which may affect salt and water absorption
- Overactive thyroid gland
- Inability to produce enough insulin or resistance to normal levels of insulin
- Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion), red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions
- Redness or pain at the injection site
- Mouth pain
- Infections or inflammation of the mouth, mouth ulcers, oesophagus, stomach and intestines, sometimes associated with pain or bleeding, poor movement of the intestines (including blockage), abdominal or oesophageal discomfort, difficulty swallowing, vomiting of blood
- Skin infections
- Bacterial and viral infections
- Tooth infection
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Inflammation or haemorrhage of the blood vessels that can appear as small red or purple dots (usually on the legs) to large bruise-like patches under the skin or tissue
- Benign cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.

Rare side effects (may affect up to 1 in 1,000 people)

- Heart problems to include heart attack, angina
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)
- Flushing
- Discoloration of the veins
- Inflammation of the spinal nerve
- Problems with your ear, bleeding from your ear
- Underactivity of your thyroid gland
- Budd–Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins)
- Changes in or abnormal bowel function
- Bleeding in the brain
- Yellow discolouration of eyes and skin (jaundice)
- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears
- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula
- Joint effusion
- Cysts in the lining of joints (synovial cysts)
- Fracture
- Breakdown of muscle fibers leading to other complications
- Swelling of the liver, bleeding from the liver
- Cancer of the kidney
- Psoriasis like skin condition
- Cancer of the skin
- Paleness of the skin
- Increase of platelets or plasma cells (a type of white cell) in the blood
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Abnormal reaction to blood transfusions
- Partial or total loss of vision
- Decreased sex drive
- Drooling
- Bulging eyes
- Sensitivity to light
- Rapid breathing
- Rectal pain
- Gallstones
- Hernia
- Injuries
- Brittle or weak nails
- Abnormal protein deposits in your vital organs
- Coma
- Intestinal ulcers
- Multi-organ failure
- Death

If you are given bortezomib together with other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Pneumonia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Mouth ulcers
- Constipation
- Muscle pain, bone pain
- Hair loss and abnormal hair texture
- Tiredness, feeling weak
- Fever

Common side effects (may affect up to 1 in 10 people)
- Shingles (localized including around the eyes or spread across the body)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- Hypersensitivity (allergic reaction)
- Inability to produce enough insulin or resistance to normal levels of insulin
- Fluid retention
- Difficulty or problems in sleeping
- Loss of consciousness
- Altered level of consciousness, confusion
- Feeling dizzy
- Increased heartbeat, high blood pressure, sweating,
- Abnormal vision, blurred vision
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath with exercise
- Cough
- Hiccups
- Ringing in the ears, ear discomfort
- Bleeding from your bowels or stomach
- Heartburn
- Stomach pain, bloating
- Difficulty swallowing
- Infection or inflammation of the stomach and intestine
- Stomach pain
- Sore mouth or lip, throat pain
- Alteration of liver function
- Itching of skin
- Redness of skin
- Rash
- Muscle spasms
- Infection of the urinary tract

- Pain in limbs
- Swelling of body, to include eyes and other parts of the body
- Shivering
- Redness and pain at injection site
- General ill feeling
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)
- Hepatitis
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Movement disorders, paralysis, twitching
- Vertigo
- Hearing loss, deafness
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Blood clots in your lungs
- Yellow discoloration of the eyes and skin (jaundice)
- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bortezomib Fresenius Kabi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP.

This medicinal product does not require any special temperature storage condition. Keep the vial in the outer carton in order to protect from light.

The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml and 2.5 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration. Bortezomib is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Bortezomib Fresenius Kabi contains

- The active substance is bortezomib.
- The other ingredients are mannitol (E421).
  Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
  Each vial contains 2.5 mg of bortezomib (as a mannitol boronic ester).

  Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
  Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester).

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

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

What Bortezomib Fresenius Kabi looks like and contents of the pack
Bortezomib powder for solution for injection is a white to off-white lyophilized powder or cake.

Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection
Each carton of Bortezomib Fresenius Kabi 2.5 mg powder for solution for injection contains a 10 ml clear glass vial with grey rubber stopper and aluminium yellow flip-off over seal, containing 2.5 mg bortezomib.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection
Each carton of Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection contains a 10 ml clear glass vial with grey rubber stopper and aluminium blue flip-off over seal, containing 3.5 mg bortezomib.

The vial is shrink wrapped (without tray) or placed in a tray with a lid. Each pack contains 1 single-use vial.

Marketing Authorisation Holder
Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

Manufacturer
Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg,
Germany

Or

Fresenius Kabi Polska Sp. z.o.o.,
ul. Sienkiewicza 25, Kutno,
99-300, Poland

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in MM/YYYY

Other sources of information
Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

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

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

1.1 **Preparation of the 2.5 mg vial: carefully add 2.5 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the bortezomib by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

Preparation of the 3.5 mg vial: carefully add 3.5 ml of sterile, sodium chloride 9 mg/ml (0.9%) solution for injection to the vial containing the bortezomib powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution must be discarded. Be sure that the correct dose is being given for the intravenous route of administration (1 mg/ml).

1.3 The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml and 2.5 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration.

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

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, sodium chloride 9 mg/ml (0.9%) solution.

Bortezomib Fresenius Kabi 2.5 mg and 3.5 mg IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material must be disposed of in accordance with local requirements.

The following information is intended for healthcare professionals only:
Only the 2.5 mg and 3.5 mg vial can be administered subcutaneously, as described below.

1. RECONSTITUTION FOR SUBCUTANEOUS INJECTION

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

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

1.1 **Preparation of the 2.5 mg vial: carefully add 1 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the bortezomib by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

Preparation of the 3.5 mg vial: carefully add 1.4 ml of sterile, sodium chloride 9 mg/ml (0.9%) solution for injection to the vial containing the bortezomib powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 2.5 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution must be discarded. Be sure that the correct dose is being given for the **subcutaneous** route of administration (2.5 mg/ml).

1.3 The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml and 2.5 mg/ml for 96 hours at 25°C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25°C) and 8 days (if stored at 2-8°C) prior to administration.

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

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use. (check that the syringe is marked as subcutaneous administration).

- Inject the solution subcutaneously, under a 45-90°angle.
- The reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left).
- Injection sites must be rotated for successive injections.
- If local injection site reactions occur following bortezomib injection subcutaneously, either a less concentrated bortezomib solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

Bortezomib Fresenius Kabi 2.5 mg and 3.5 mg IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

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

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