Bortezomib

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MIBZO

3.5 mg Lyophilized Powder for Injection (IV/SC)
Antineoplastic Agent (Proteasome Inhibitor)

Name of the medicinal Product
Bortezomb For Injection 3.5 mg/vial.

Dosage Forms And Strength
For injection : Single-dose vial contains 3.5 mg of Bortezomb as lyophilized powder for reconstitution and withdrawal of the appropriate individual patient dose .

Pharmacological Category : Antineoplastic agents, other antineoplastic agents, ATC code L01XX32

Product Description
Lyophilized powder for injection 3.5 mg/vial
White to off white lyophilized cake or powder in 10 ml tubular USP Type-1 clear vial with 13 mm bromobutyl double slotted rubber stopper and sealed 13 mm aluminium seal having polypropylene disc

Formulation / Composition
Bortezomb For Injection 3.5 mg/vial
Each Vial contains ..... Bortezomb 3.5 mg
After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg Bortezomb.
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg Bortezomb.
For the full list of excipients, see Pharmaceutical particulars

Pharmacodynamics

Mechanism of action
Bortezomb 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 important 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.
Bortezomb is highly selective for the proteasome. At 10 μM concentrations, Bortezomb 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 Bortezomb was shown to dissociate from the proteasome with a t½ of 20 minutes, thus demonstrating that proteasome inhibition by Bortezomb is reversible.
Bortezomb 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 tumorigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, Bortezomb affects the ability of myeloma cells to interact with the bone marrow microenvironment.
Experiments have demonstrated that Bortezomb 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. Inhibition of proteasome activity in tumour growth in vivo in many preclinical models, including multiple myeloma.
Bortezomb enhances the activity of dexamethasone. Bortezomb is suggested that it increases celecoxibal differentiation and activity and inhibits celecoxibal function. These effects have been observed in patients with multiple myeloma affected by an advanced celecoxibic disease and treated with Bortezomb

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 Bortezomb (1.3 mg/m2 injected intravenously) in combination with melphalan (9 mg/m2) and prednisone (60 mg/m2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m2) and prednisone (60 mg/m2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 1 year). Bortezomb was administered twice weekly for four consecutive weeks followed by a two week rest period. The median age was 71 years (range: 40 - 93 years), 64% were Caucasian and the median Karnofsky performance status score the patients was 80. Patients had IgG/IgA/Light chain myeloma in 62%/23%/8% instances, a median serum-globin of 108 g/l, and a median platelet count of 221.5 x 109/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 proportion of patients with a time to progression, was met and patients in the M+P arm were offered the VMP 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 Vc+M+P treatment group was observed (hazard ratio (HR)=0.695; p=0.00043) despite subsequent therapies including Bortezomb-based regimens. Median survival for the Vc+M+P treatment group was 56.4 months compared to 43.1 for the M+P treatment group. Efficacy results are presented in Table 1

Table 1 : Efficacy results following the final survival update to VISTA study

Efficacy endpoint	M+P n=344	M+P n=338
Time to progression Events n (%)	151 (29)	152 (45)
Median† (95% CI)	20.7 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio* (95% CI)	0.54 (0.42, 0.70)	
p-value‡	0.000002	
Progression-free survival Events n (%)	126 (36)	190 (56)
Median† (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio* (95% CI)	0.61 (0.48, 0.76)	
p-value‡	0.00001	
Overall survival* Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median† (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio* (95% CI)	0.695 (0.567, 0.852)	
p-value‡	0.00043	
Response rate population† n=668	n=337	n=331
CR* n (%)	102 (30)	12 (4)
PR* n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR+PR* n (%)	238 (71)	115 (35)
p-value‡	< 10^{-16}	
Reduction in serum M-protein population† n=657	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† response duration		
CR*	24.0 mo	12.8 mo
CR+PR*	19.9 mo	13.1 mo
Time to next therapy Events n (%)	224 (65.1)	260 (76.9)
Median† (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio* (95% CI)	0.557 (0.462, 0.671)	
p-value‡	< 0.000001	

*Kaplan-Meier estimate.
†Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors. IL-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
‡ Nominal p-value based on the stratified log-rank test adjusted for stratification factors. IL-microglobulin, albumin, and region
† p-value for Response Rate (CR+PR) from the Cochran Mantel-Haenszel chi-square test adjusted for the stratification factors
* Response population includes patients with measurable disease at baseline
*CR=Complete Response; PR=Partial Response, EBMT criteria
* All randomized 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 Bortezomb in dual and triple combinations with other chemotherapeutic and biotherapeutic agents, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma.
In study IFM-2005-01 Bortezomb combined with dexamethasone [VcDx, n=240] was compared to vincristine- doxorubicin-dexamethasone [VDDx, n=242]. Patients in the VcDx group received four 21 day cycles, each consisting of Bortezomb (1.3 mg/m2administered 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 VcDx groups respectively; the majority of patients underwent one single transplant procedure. Patient demographic and baseline disease characteristics were similar between the treatment groups. Median age of the patients in the study was 57 years, 55% were male and 48% of patients had high-risk cytogenetics. The median duration of treatment was 13 weeks for the VDDx group and 11 weeks for the VcDx group. The median number of cycles received for both groups was 4 cycles.
The primary efficacy endpoint of the study was pre-induction response rate (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the Bortezomb 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 2

Table 2 : Efficacy results from study IFM-2005-01

Endpoints	BDx	VDDx	**OR; 95% CI; P value***
IFM-2005-01	N=240 (ITT population)	N=242 (ITT population)	
RR (Post-induction) †CR+CR ‡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, 3.26); < 0.001
RR(Post-transplant)† 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= Bortezomb; BDx= Bortezomb, dexamethasone; VDDx=vincristine, doxorubicin, dexamethasone; VGPR=very good partial response; PR=partial response, OR=odds ratio.
*Cochran-Mantel-Haenszel
* OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.
† 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 IMM-3010 induction treatment withBortezomb combined with thalidomide and dexamethasone [VcTDx, n=130] was compared to thalidomide-dexamethasone [TDx, n=127]. Patients in the VcTDx group received six 4-week cycles, each consisting of Bortezomb (1.3 mg/m2administered 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 9 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 VcTDx and TDx groups, respectively. Patient demographic and baseline disease characteristics were similar between the treatment groups. Patients in the VcTDx and TDx groups respectively had a median age of 57 versus 58 years, 59% versus 68% patients were Caucasians, and 58% versus 54% were males. In the VcTDx 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 Bortezomb combined with dexamethasone and thalidomide group. Secondary efficacy endpoints included Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 3

Table 3: Efficacy results from study MMY-3010

Endpoints	BTDx	TDx	**OR; 95% CI; P value***
MMY-3010	N=130 (ITT population)	N=127 (ITT population)	
*RR (Post-induction) CR+nCR CR+nCR+PR % (95% CI)	49.2 (40.4, 58.1) 84.6 (77.2, 90.3)	17.3 (11.2, 25.0) 61.4 (52.4, 69.9)	4.83 (2.61, 9.22); < 0.001* 3.46 (1.90, 6.27); < 0.001*
*RR (Post-transplant) CR+nCR CR+nCR+PR % (95% CI)	55.4 (46.4, 64.1) 77.7 (69.6, 84.5)	34.6 (26.4, 43.6) 56.7 (47.6, 65.5)	2.34 (1.42, 3.87); 0.001* 2.68 (1.55, 4.57); < 0.001*

CI=confidence interval; CR=complete response; nCR=near complete response; ITT = intent to treat; RR= response rate; B= Bortezomb; BTDx= Bortezomb, thalidomide, dexamethasone; TDx=thalidomide, dexamethasone ; PR=partial response; OR=odds ratio
* Primary endpoint
* OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.

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

Clinical efficacy in relapsed or refractory multiple myeloma
The safety and efficacy of Bortezomib (injected intravenously) were evaluated in 2 studies at the recommended dose of 1.3 mg/m2: 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 Bortezomb led to a significantly longer time to progression, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone , 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 Bortezomb, 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 Bortezomb 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 Bortezomb independently of age. Regardless of β2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the Bortezomb 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% (15/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67).

Table 4 : Summary of disease outcomes from the Phase III (APEX) and Phase II studies

	Phase III	Phase III	Phase III	Phase II
All patients	All patients	1 prior line of therapy	> 1 prior line of therapy	**≥ 2 prior lines**

Time related events	B n=**333***	Dex n=**336***	B n=**132***	Dex n=**119***	B n=**200***	Dex n=**217***	B n=**202***
TTP, days [95% CI]	189* [148, 211]	106* [86, 128]	212* [168, 267]	169* [106, 191]	148* [126, 182]	87* [84, 107]	210 [154, 281]
1 year survival, % [95% CI]	80* [74,85]	69* [59,72]	89* [82,95]	72* [62,83]	73 [64,82]	62 [53,71]	60
Best response (%)	B n=**315***	Dex n=**312***	B n=128	Dex n=110	B n=187	Dex n=202	B n=193
CR	20 (6)*	2 (< 1)*	8 (6)	2 (2)	12 (6)	0 (0)	(4)**
CR+nCR	41 (13)*	5 (2)*	16 (13)	4 (4)	25 (13)	1 (< 1)	(10)**
CR+nCR+PR	121 (38)*	56 (18)*	57 (45)*	29 (26)*	64 (34)*	27 (13)*	(27)**
CR+nCR+PR+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	65 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	138 (4.1)	385*
Time to response CR+PR (days)	43	43	44	46	41	27	38*

*Intent to Treat (ITT) population
† p-value from the stratified log-rank test, analysis by line of therapy excludes stratification for therapeutic history; p < 0.0001
* Response population includes patients who had measurable disease at baseline and who received at least 1 dose of study medicinal product.
† 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+PR, (IF CR=CR) (IF r)
NA=not applicable, ND=not estimated
TTP=Time to Progression
CI=Confidence Interval
B=Bortezomb; Dex=dexamethasone
CR=Complete Response; nCR=near Complete response
PR=Partial Response; MR=Minimal response

with Bortezomb. The protocol allowed patients to receive dexamethasone if they had had a less than optimal response to Bortezomb alone. A total of 74 evaluable patients were administered dexamethasone in combination with Bortezomb. Eighteen percent of patients achieved, or had an improved response [MR (11%) or PR (7%)], with combination treatment.
Clinical efficacy with subcutaneous administration of Bortezomb in patients with relapsed/refractory multiple myeloma An open-label, randomised, Phase III non-inferiority study comparing the efficacy and safety of the subcutaneous administration of Bortezomb versus the intravenous administration. This study included 222 patients with relapsed multiple myeloma, who were randomised in a 2:1 ratio to receive 1.3 mg/m2 of Bortezomb 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 Bortezomb alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and after Bortezomb administration. Patients with baseline Grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/μl were excluded. A total of 218 patients received treatment.
This study met its primary objective of non-inferiority for response rate (CR+PR) after 4 cycles of single agent Bortezomb both the subcutaneous and intravenous routes. 42% in both groups. In addition, secondary responsemeasures also showed to be event related efficacy endpoint showed consistent results for subcutaneous and intravenous administration (Table 5).

Table 5 : Summary of efficacy analyses comparing subcutaneous and intravenous administrations of Bortezomb

Response Evaluable Population	**Bortezomib intravenous arm** n=**73**	Bortezomib subcutaneous arm n=145
Response Rate at 4 cycles n (%)		
CRR (CR+PR)	31 (42)	61 (42)
p-value*	0.00201	
CR n (%)	6 (8)	9 (6)
PR n (%)	25 (34)	52 (36)
nCR n (%)	0 (45)	9 (8)
Response Rate at 8 cycles n (%)		
CRR (CR+PR)	38 (52)	76 (52)
p-value*	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29 (40)	61 (42)
nCR n (%)	7 (10)	14 (10)
Intent to Treat Population†	n=74	n=148
TTP months	9.4	10.4
(95% CI)	(7.6, 10.6)	(8.5, 11.7)
p-value‡	0.639 (0.564, 1.248)	
Progression Free Survival, months	8.0	10.2
(95% CI)	(6.7, 8.8)	(8.1, 10.8)
Hazard ratio (95% CI)*	0.824 (0.574, 1.183)	
p-value‡	0.295	
1-year Overall Survival (%)*	76.7	72.6
(95% CI)	(64.1, 85.4)	(63.1, 80.3)

* p-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.
† 222 subjects were enrolled into this study. 221 subjects were treated at least once.
‡ Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.
* Log rank test adjusted for stratification factors: ISS staging and number of prior lines.
* Median duration of follow up is 11.8 months

Bortezomb combined 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 Bortezomb plus pegylated liposomal doxorubicin versus Bortezomb 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 24-61%, p < 0.0001) in the patients treated with Bortezomb plus pegylated liposomal doxorubicin. The median TTP was 6.5 months for the Bortezomb monotherapy patients compared with 9.3 months for the Bortezomb plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the pre-specified 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 Bortezomb monotherapy patients and 33.0 months (95% CI: 28.9-37.1 months) for the Bortezomb plus pegylated liposomal doxorubicin combination therapy patients.
*Bortezomb combined with dexamethasone
In the absence of any direct comparison between Bortezomb and Bortezomb 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 Bortezomb in combination with dexamethasone (Phase II open-label study MMY-2045), with results obtained in the Bortezomb monotherapy arm from different Phase III randomised studies (APEX/ CR-209 [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. Bortezomb in combination with dexamethasone) and patients in the comparison group (e.g. Bortezomb) 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 2.545-6.947; p < 0.001), PFS (hazard ratio 0.51; 95 CI 0.309-0.845; p=0.008), TTP (hazard ratio 0.385; 95% CI 0.212-0.698; p=0.001) for Bortezomb in combination with dexamethasone over Bortezomb monotherapy.
*Limited information on Bortezomb 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 Bortezomb. One hundred and thirty patients (≥ 18 years of age) with multiple myeloma who previously had at least partial response on a Bortezomb-containing regimen were retreated upon progression. At least 6 months after prior therapy, Bortezomb was started at the last tolerated dose of 1.3 mg/m2 (n=93) or ≤ 1.0 mg/m2 (n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamone was administered in combination with Bortezomb to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of Bortezomb 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 Bortezomb, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in 240 in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR-CAP treatment arm received Bortezomb (1.3 mg/m2, on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m2 IV on day 1, cyclophosphamide 750 mg/m2 IV on day 1, doxorubicin 50 mg/m2 IV on day 1, and prednisone 100 mg/m2orally on day 1 through day 5 of the 21 day Bortezomb treatment cycle. For patients with a response first documented at cycle 8, 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 (CRCRu) rate, overall survival (OS) and time to failure.
The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 68% were Caucasian and 24% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow trephine biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 76% had Stage III-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 VcR-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 VcR-CAP group and 82% in the R-CHOP group. Efficacy results are presented in Table 6.

Table 6: Efficacy results from study LYM-3002

Efficacy endpoint	BR-CAP	R-CHOP	
n: ITT patients	243	244	
Progression free survival (IRC)*			
Events n (%)	133 (54.7%)	165 (67.6%)	HR*; 95% CI=0.63 (0.50; 0.79) p-value* < 0.001
Median† (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* n(%)	122 (53.3%)	95 (41.7%)	OR*; 95% CI=1.688 (1.148; 2.481) p-value=0.007
Overall response CR+CRu+PR‡ n(%)	211 (92.1%)	204 (89.5%)	OR*; 95% CI=1.428 (0.749; 2.722) p-value=0.275

Based on Independent Review Committee (IRC) assessment (radiological data only).
* 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.
† Based on Kaplan-Meier product limit estimates.
* Based on Log rank test stratified with IPI risk and stage of disease.
* 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.
*Include all CR+CRu, by IRC, bone marrow and LDH.
† P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.
‡ 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 52 months. Median OS was 90.7 months for the BR-CAP group compared with 55.7 months in the R-CHOP group (HR=0.66, p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

Patients with previously treated light chain (AL) Amyloidosis
An open-label non randomised Phase III study was conducted to determine the safety and efficacy of Bortezomb in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular Bortezomb did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis, a 87.3% 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 dose of 1.6 mg/m2 weekly and 1.3 mg/m2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Bortezomb in all subsets of the paediatric population in multiple myeloma and in mantle cell lymphoma.

A Phase II, single-arm activity, safety, and pharmacokinetic trial conducted by the Children's Oncology Group assessed the activity of the addition of Bortezomb to multi-agent re-induction chemotherapy in paediatric and young adult patients with lymphoid malignancies (pre-B cell acute lymphoblastic leukemia [ALL], T-cell ALL, and T-cell lymphoblastic lymphoma [LL]). An effective re-induction multi-agent chemotherapy regimen was administered in 3 blocks. Bortezomb 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
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 Bortezomb 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 Bortezomb 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 3%), 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), hypokalemia (18% versus 6% in Block 1 and 21% versus 12% in Block 2) and hyperbilirubinemia (12% versus 5% in Block 1 and 4% versus 0 in Block 2).

Pharmacokinetics
Absorption
Following intravenous bolus administration of a 1.0 mg/m2 and 1.3 mg/m2 dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of Bortezomb 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/m2 dose and 89 to 135 ng/ml for the 1.3 mg/m2 dose.
Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m2 dose to patients with multiple myeloma (n=14 in the intravenous group, n=17 in the subcutaneous group) the total systemic exposure after repeat administration (AUCtotal) was equivalent for subcutaneous and intravenous administrations. The Cmax after subcutaneous administration (20.4 ng/ml) was lower than that after intravenous (225 ng/ml). The AUCtotal geometric mean ratio was 0.99 and 90% confidence intervals were 60.18%-122.82%.
Distribution
The mean distribution volume (Vd) of Bortezomb ranged from 1,659 l to 3,294 l following single- or repeated-dose intravenous administration of 1.0 mg/m2 or 1.3 mg/m2 to patients with multiple myeloma. This suggests that Bortezomb distributes widely to peripheral tissues. Over a Bortezomb concentration range of 0.01 to 1.0 μg/ml, the in vitro protein binding averaged 82.9% in human plasma. The fraction of Bortezomb 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 Bortezomb is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-Bortezomb metabolites are inactive as 26S proteasome inhibitors.

Elimination
The mean elimination half-life (t½) of Bortezomb upon multiple dosing ranged from 40-193 hours. Bortezomb 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/m2 and 1.3 mg/m2, respectively, and ranged from 15 to 32 l/h and 15 to 32 l/h following subsequent doses for doses of 1.0 mg/m2 and 1.3 mg/m2, respectively.
Special populations
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of Bortezomb 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 Bortezomb doses ranging from 0.5 to 1.3 mg/m2 .
When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized Bortezomb AUC. However, the dose-normalized 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 monitoredfinal 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 ≥ 80 ml/min/1.73 m2, n=12), Mild (CrCL=50-69 ml/min/1.73 m2, n=10), Moderate (CrCL=20-38 ml/min/1.73 m2, n=8), and Severe (CrCL < 20 ml/min/1.73 m2, n=9). A group of dialysis patients who were dosed after dialysis was also included in the study (n=6). Patients were administered intravenous doses of 0.7 to 1.3 mg/m2 of Bortezomb twice weekly. Exposure of Bortezomb (dose-normalised AUC and Cmax) was comparable among all the groups.
Age
The pharmacokinetics of Bortezomb were characterized following twice weekly intravenous bolus administration of 1.3 mg/m2doses 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 Bortezomb increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hm2, volume of distribution at steady-state was 834 (39%) L/m2, and the elimination half-life was 100 (64%) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on Bortezomb clearance. BSA-normalized clearance of Bortezomb in pediatric patients was similar to that observed in adults.

Preclinical safety data
Bortezomb 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. Bortezomb was not genotoxic when tested in the in vitro mutagenicity assay (Ames assay) and in vivo micronucleus assay in mice.
Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed 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 Bortezomb could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.
In repeated dose toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; hematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lympho

- 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 11 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 11: 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 withheld, 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/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²).
• ≥ 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/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For Bortezomib- related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib as outlined in Table 7.

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 in 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, VIPCAP as well as R-CHOP, were less tolerated.

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/m2 per patient during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² may be considered based on patient tolerability (see Table 6 and sections 4.4 and 5.2).

Table 12: 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-3x ULN	Any	Reduce Bortezomib to 0.7 mg/m² in the first treatment cycle. Consider dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² 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 categorizing 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 m²); 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 m²). Since dialysis may reduce Bortezomib concentrations, Bortezomib should be administered after the haemodialysis session.

Paediatric population
The safety and efficacy of Bortezomib in children below 18 years of age have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made

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.

WARNINGS AND PRECAUTIONS

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.

Intrathecal administration
There have been fatal cases of inadvertent intrathecal administration of Bortezomib. Bortezomib 1 mg powder for solution for injection is for intravenous use only, while Bortezomib 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. 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 (VcR-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 (VcR-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 (8.3% in the VcR-CAP group and 5.3% in the R-CHOP group) as well as Grade 3 and higher bleeding events (VcR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the VcR-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. Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for haemorrhage.
Full 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.
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 VcR-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.

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 VcR-CAP arm and 1.2% in the R-CHOP arm.

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, paresthesia, 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=0.0254). 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. 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 therapeutic 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 and 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 the clinical 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. 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 case 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/m² 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/m² per day) by continuous infusion over 24 hours is not recommended

Renal impairment
Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely.

Hepatic impairment
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.

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.

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.
Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics

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.
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% (CI60% [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 weak 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.
In 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 therapy may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics

Fertility, pregnancy and lactation

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

Pregnancy
No clinical data are available for Bortezomib with regard to exposure during pregnancy. The teratogenic potential of Bortezomib has not been fully investigated.
In non-clinical studies, Bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of Bortezomib on parturition and post-natal development were not conducted. 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.

Drug Interaction

Effects of other Drugs on Bortezomib For injection 3.5 mg/vial Strong CYP3A4 Inducers
Coadministration with a strong CYP3A4 inducer decreases the exposure of Bortezomib which may decrease Bortezomib For Injection 3.5 mg/vial efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors
Coadministration with a strong CYP3A4 inhibitor increases the exposure of Bortezomib which may increase the risk of Bortezomib For Injection 3.5 mg/vial toxicities. Monitor patients for signs of Bortezomib toxicity and consider a Bortezomib dose reduction if Bortezomib must be given in combination with strong CYP3A4 inhibitors.
Drugs Without Clinically Significant Interactions with Bortezomib For Injection 3.5 mg/vial
No clinically significant drug interactions have been observed when Bortezomib For Injection 3.5 mg/vial was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone

ADVERSE DRUG REACTIONS

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

Tabulated summary of adverse reactions
Multiple Myeloma
Undesirable effects in Table 7 were considered by the investigators to have at least a possible or probable causal relationship to Bortezomib. These adverse reactions are based on an integrated data set of 5,476 patients of whom 3,996 were treated with Bortezomib at 1.3 mg/m2 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 13: 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	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	Dyspnea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hypotrihidrosis*, 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.
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 reactivation & 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 15: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		MMY-3010		
	VDDx	BDx	TDx	BTDx	BTDx
	(N=239)	(N=239)	(N=126)	(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 (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 16: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	BR-CAP	R-CHOP
	(N=240)	(N=242)
Incidence of PN (%)		
All 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 events 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%-18% 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.
The incidence of injection site reactions was higher in the subcutaneous administration, mostly redness. Cases resolved in a median of 8 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 8% 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 20% 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.

OVERDOSE AND TREATMENT

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

STORAGE CONDITION

Store at temperatures not exceeding 30°C.
Protect from light and moisture
Keep out of reach of children

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibited dispensing without Prescription .

ADR REPORTING STATEMENT

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Instruct patient to seek medical attention immediately at the first sign of any adverse drug reaction.

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