janssen

VELCADE®
bortezomib

QUALITATIVE AND QUANTITATIVE COMPOSITION
Velcade (bortezomib) for Injection is an antineoplastic agent available for intravenous injection (IV) or subcutaneous (SC). Each single use vial contains:

- 1.0 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 10 mg mannitol, USP/EP (IV use only), or
- 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP/EP (IV or SC use).

PHARMACEUTICAL FORM
Velcade (bortezomib) for Injection is supplied as individually cartooned 5 mL vials containing 1 mg of bortezomib, or 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

- 1.0 mg single use vial
- 3.5 mg single use vial

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Mechanism of Action
Bortezomib is a reversible inhibitor of 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 intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death**.** Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor 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 Trials
Phase 2 Clinical Studies in Relapsed Multiple Myeloma:
The safety and efficacy of Velcade IV were evaluated in an open-label, single-arm, multicenter study (M34100-25) of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in Table 1.

An IV bolus injection of Velcade 1.3 mg/m^2/dose was administered twice weekly for 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity (see *Posology and Method of Administration*). Patients who experienced a response to Velcade treatment were allowed to continue Velcade treatment in an extension study.

Table 1: Summary of Multiple Myeloma Patient Population and Disease Characteristics[a]

	N = 202
Patient Characteristics	
Median age in years (range)	59 (34, 84)
Gender: Male-Female	60% /40%
Race: Caucasian/black/other	81% / 10% / 8%
Karnofsky Performance Status score ≤ 70	20%
Hemoglobin < 100 g/L	44%
Platelet count < 75 x 10^9/L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β2-microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9

Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MG, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplantation/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

[a] Based on number of patients with baseline data available

Responses to Velcade alone are shown in Table 2. Response rates to Velcade alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others. Complete response required <5% plasma cells in the marrow, 100% reduction in M protein, and a negative immunofixation test (IF^-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥75% reduction in serum myeloma protein and/or ≥90% urine protein. A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2 administered IV. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while 33% of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patient who had a confirmed CR received 2 additional cycles of Velcade treatment beyond confirmation. It was recommended that responding patients receive up to 8 cycles of Velcade therapy. The mean number of cycles administered was 6.

The median time to response was 38 days (range 30 to 127 days).
The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

Table 2: Summary of Disease Outcomes

Response Analyses (Velcade monotherapy) N = 188	**N (%)**	**(95%, CI)**
Overall Response Rate (Blade) (CR + PR)	52 (27.7%)	(21.35)
Complete Response (CR)[1]	5 (2.7%)	(1.6)
Partial Response (PR)[2]	47 (25%)	(19.32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12.24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

1 Complete Response required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-).

2 Partial Response requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

3 Clinical Remission (SWOG) required ≥75% reduction in serum myeloma protein and/or ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

In this study, the response rate to Velcade was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study (M34100-24) was performed in 54 patients with multiple myeloma who received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

Patients who did not obtain an optimal response to therapy with Velcade alone (progressive or stable disease after 2 or 4 cycles, respectively) were able to receive high-dose dexamethasone in conjunction with Velcade (i.e., 40 mg dexamethasone with each dose of Velcade administered orally as 20 mg on the day of and 20 mg the day after Velcade administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160 mg over 3 weeks). A total of 74 patients were administered dexamethasone in combination with Velcade and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response

(CR 11% or PR 7%) with combination treatment.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing Velcade to Dexamethasone:
A prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial [M34101-039 (APEX)] enrolling 669 patients was designed to determine whether Velcade resulted in improvement in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline grade ≥ 2 peripheral neuropathy or platelet counts <50,000/µL. A total of 627 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had previously received (1 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during or within 6 months of stopping their most recent therapy versus relapse >6 months after receiving their most recent therapy), and screening β_2-microglobulin levels (≤2.5 mg/L versus >2.5 mg/L).

Baseline patient and disease characteristics are summarized in Table 3.

Table 3: Summary of Baseline Patients and Disease Characteristics in the Phase 3 APEX Trial

Patient Characteristics	**Velcade N = 333**	**Dexamethasone N = 336**
Median age in years (range)	62.0 (33.84)	61.0 (27.86)
Gender: male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin < 100 g/L	32%	28%
Platelet count < 75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%) IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β2-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n(%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
> 1 prior line	60%	65%
All Patients	(N = 333)	(N = 336)
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

Patients in the Velcade treatment group were to receive eight 3-week treatment cycles followed by three 5-week treatment cycles of Velcade. Within each 3-week treatment cycle, Velcade 1.3 mg/m^2/dose alone was administered by IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment cycle, Velcade 1.3 mg/m^2/dose alone was administered by IV bolus once weekly for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35) (see *Posology and Method of Administration*).

Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15-day rest period (Days 21 to 35). Within each 4-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered Velcade at a standard dose and schedule on a companion study.

Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients

randomized to dexamethasone were offered Velcade, regardless of disease status. At this time of study termination, a final statistical analysis was performed. Due to this early termination of the study, the median duration of follow-up for surviving patients (n=534) is limited to 8.3 months.

In the Velcade arm, 34% of patients received at least one Velcade dose in all 8 of the 3- week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number of Velcade doses during the study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all 4 of the 5-week treatment cycles of therapy, and 6% received at least one dose in all 9 cycles.

The time to event analyses and response rates from the phase 3 trial are presented in Table 4. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Partial Response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis, however M-protein was still detectable by immunofixation (IF^+).

Table 4: Summary of Efficacy Analyses in the Randomized Phase 3 APEX Study

	All patients		**1 Prior Line of Therapy**		**> 1 Prior 1 Line of Therapy**	
	Velcade	**Dex**	**Velcade**	**Dex**	**Velcade**	**Dex**
Efficacy Endpoint	**N = 333**	**N 336**	**N = 132**	**N = 119**	**Nn = 200**	**N = 217**
Time to Progression						
Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (2.8, 3.5)
Hazard ratio [b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value [c]	< 0.0001		0.0019		< 0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
p-value [c, d]	< 0.05		< 0.05		< 0.05	
Response Rate						
Population [e] n = 627	N = 315	N = 312	N = 128	N = 110	N = 187	N = 202
CR [f] n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PF [f] n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR [f,g] n (%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR [f] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value [h]	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR [f]	9.9 mo	NE l	9.9 mo	NE	6.3 mo	NA l
nCR [f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR [f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[a] Kaplan-Meier estimate.

[b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for Velcade.

[c] p-value based on the stratified log-rank test including randomization stratification factors.

[d] Precise p-value cannot be rendered

[e] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.

[f] EBMT criteria[2]; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria, nCR is in the PR category.

[g] In 2 patients, the IF was unknown.

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

[i] Not Estimable.

[j] Not Applicable, no patients in category.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing Velcade IV and SC

An open-label, randomized, phase 3 non-inferiority study (MMY-3021) compared the efficacy and safety of the subcutaneous administration (SC) of Velcade versus the intravenous administration (IV). This study included 222 patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of Velcade by either the SC or IV route for 8 cycles. Patients who did not obtain an optimal response (less than Complete Response (CR)) to therapy with Velcade alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and after Velcade 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.

Stratification factors were based on the number of lines of prior therapy the patient had received (1 previous line versus more than 1 line of therapy), and international staging system (ISS) stage (incorporating beta2-microglobulin and albumin levels; Stages I, II, or III).

Baseline patient and disease characteristics are summarized in Table 5.

Table 5: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of Velcade IV vs SC (MMY-3021)

Patient Characteristics	**IV N=74**	**SC N=148**
Median age in years (range)	64.5 (38.86)	64.5 (42.88)
Gender: male/female	64%/36%	50%/50%
Race: Caucasian/Asian	96%/4%	97%/3%
Karnofsky performance status score ≤ 70	16%	22%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	72%/19%/8%	65%/26%/8%
ISS staging[a] I/II/III (%)	27/41/32	27/41/32
Median β2-microglobulin (mg/L)	4.25	4.20
Median albumin (g/L)	3.60	3.55
Creatinine clearance ≤ 30 mL/min [n (%)]	2 (3%)	5 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	2.93	2.68
Number of Prior Therapeutic Lines of Treatment		
1 prior line	65%	62%
> prior line	35%	38%

[a] ISS Staging is derived from baseline central laboratory data.

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent Velcade for both the SC and IV routes, 42% in both groups. In addition, secondary response-related and time to event related efficacy endpoints showed consistent results for SC and IV administration (Table 6).

Table 6: Summary of efficacy analyses for the SC administration of Velcade compared to IV (MMY-3021)

Response-Evaluable Population [a]	**IV Velcade N=73**	**SC Velcade N=145**
Response Rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value [b]	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		
ORR (CR+PR)	38 (52)	76 (52)
p-value [b]	0.0001	
CR n (%)	9(12)	15(10)
PR n (%)	29(40)	61(42)
nCR n (%)	7(10)	14(10)
Intent to Treat Population [c]	**N=74**	**N=148**
Median Time to Progression, months	9.4	10.4
(95% CI)	(7.6, 10.6)	(8.5, 11.7)
Hazard ratio (95% CI) [d]	0.839 (0.564, 1.249)	
p-value [e]	0.38657	
Progression Free Survival, months	8.0	10.2
(95% CI)	(6.7, 9.8)	(8.1, 10.8)

Hazard ratio (95% CI) [d]	0.824 (0.574, 1.183)	
p-value [d]	0.295	
1-year Overall Survival (%) [f]	76.7	72.6
(95% CI)	(64.1, 85.4)	(63.1, 80.19)

[a] All randomized subjects who received at least 1 non-zero dose of study medication and had measurable disease at study entry
[b] P-value is for the non-inferiority hypothesis that the SC arm at least 60% of the response rate in the IV arm
[c] 222 subjects were enrolled into the study; 221 subjects were treated with Velcade
[d] Hazards ratio estimate is based on a Cox model adjusted for stratification factors; ISS staging and number of prior lines
[e] Log rank test adjusted for stratification factors; ISS staging and number of prior lines
[f] Median duration of follow up is 11.8 months

Table 7 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after cycle 4.

Dexamethasone had a similar effect on improvement of response on both treatment arms:
- 30% (SC) and 30% (IV) of patients with no response at end of Cycle 4 obtained a response later. In subsequent cycles (cycle 5 through 8).
- 13% (SC) and 13% (IV) of patients with PR at end of Cycle 4 obtained a CR later. In subsequent cycles (cycle 5 through 8).

Table 7: Cross-tabulation of Summary of Best Response After 4 Cycles vs. After 8 Cycles for patients who received dexamethasone

		------- Best Response After 8 Cycles ------- (N=121)		
Treatment Group	Total	-------- Category, n (%) ---------		
Cycle 4 Best Response *	N (%)	CR	PR	Non-responder
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)	0	0
PR	31 (26)	4 (13)	27 (87)	0
Non-responder	47 (39)	0	14 (30)	33 (70)

*Response assessment by validated computer algorithm. This algorithm incorporates a consistent assessment of all data required for response by the modified EBMT criteria.

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from cycle 5 onwards, were higher than observed in prior registration study with single agent IV Velcade (38% ORR and median TTP of 6.2 months for the Velcade arm). Time to Progression and ORR was also higher compared to the subgroup of patients that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (**Table 4**).

VELCADE Retreatment in Relapsed Multiple Myeloma

Study MMY-2036 (RETRIEVE) was an open-label, multicenter study designed to determine the efficacy and safety of retreatment with VELCADE in 130 patients with relapsed multiple myeloma. Patients had previously tolerated 1.0 or 1.3 mg/m^2 VELCADE alone or in combination with other agents, had CR or PR upon completion of VELCADE therapy and subsequently relapsed.
As assessed by EBMT criteria, the primary endpoint of best response was achieved in 40% of patients who had a response of PR or better including 1% of whom had a best response of CR. In these 40% of patients (n=50) who had a best response of PR or better, the median time to progression (TTP) was 8.4 months (range: 3.3 to 20.7 months). The median duration of response in these patients was 6.5 months (range: 0.6 to 19.3 months).

VELCADE Combination Treatment with Pegylated Liposomal Doxorubicin

A Phase 3 randomized, parallel-group, open-label, multicentre study (DOXIL-MMY-3001) was conducted in 646 patients comparing the safety and efficacy of VELCADE plus pegylated liposomal doxorubicin combination therapy with VELCADE 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.

There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of VELCADE and pegylated liposomal doxorubicin. 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 %), $p < 0.0001$. The median TTP was 6.5 months for the VELCADE monotherapy patients compared with 9.3 months for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma:
A prospective phase 3, international, randomized (1:1), open-label clinically study [MMY-3002 (VISTA)] of 682 patients was conducted to determine whether Velcade (1.3 mg/m^2) 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. This study included patients who were not candidates for stem-cell transplant. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in Table 8.

Table 8: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**VMP N=344**	**MP N=338**
Median age in years (range)	71.0 (57.90)	71.0 (48.91)
Gender: male/female	51%/49%	49%/51%
Race: Caucasian/Asian/black/other	88%/10%/1%/1%	87%/11%/2%/0%
Karnofsky performance status score ≤ 70	35%	33%
Hemoglobin < 100 g/L	37%	36%
Platelet count < 75 x 10^9/L	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64%/24%/8%	62%/26%/8%
Median β2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤ 30 mL/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VcMP treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up at 60.1 months. A statistically significant survival benefit in favor of the VcMP treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies that included Velcade-based regimens. The median survival in MP treatment group has been estimated at 43.1 months, and the median survival on the VcMP treatment group has been estimated at 56.4 months. Efficacy results are presented in Table 9.

Table 9: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**VMP n=344**	**MP 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[f] + 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)	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis that was performed at a median follow-up duration of 60.1 months.

a Kaplan-Meier estimate

b Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta2-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: beta2-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

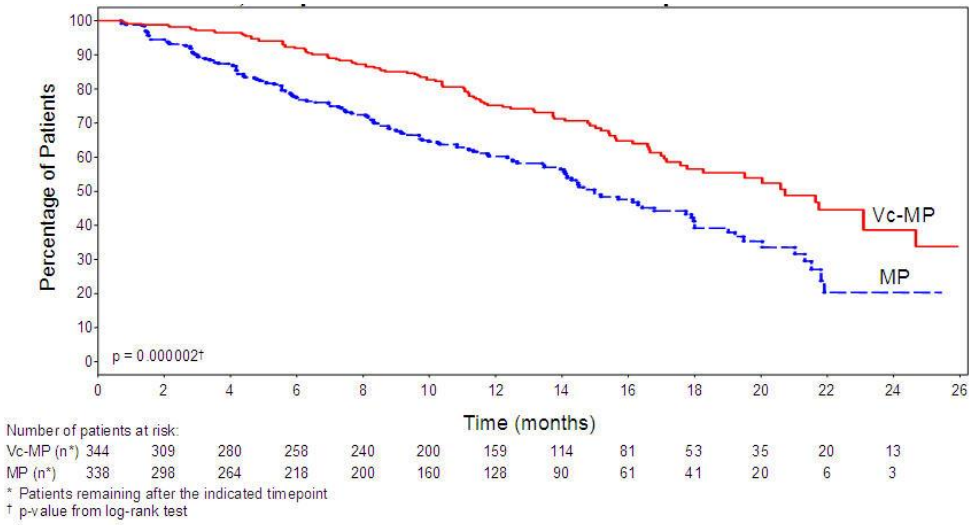
f EBMT criteria

g All randomized patients with secretory disease

* Survival update based on a median duration of follow-up at 60.1 months

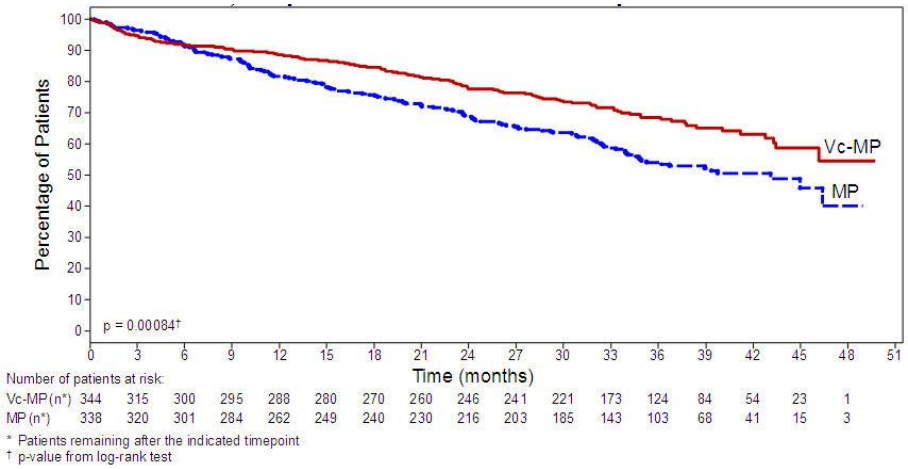
NE: Not estimable

TTP was statistically significantly longer on the VELCADE, Melphalan and Prednisone arm (see Figure 1). (median follow up 16.3 months)



Overall survival was statistically significantly longer on the VELCADE, Melphalan and Prednisone arm (see Figure 2). (median follow up 36.7 months)

Figure 2: Overall Survival
VELCADE, Melphalan and Prednisone vs Melphalan and Prednisone



Previously Untreated Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation

An integrated data analysis was conducted of three phase 3 trials (MMY-3003, IFM-2005-01, MMY-3010) to demonstrate the safety and efficacy of VELCADE, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma. These studies were similar in design (randomized, open-label, multicenter) and included 1572 patients (men and women up to 65 years of age with previously untreated multiple myeloma [Durie-Salmon stage II or III] and ECOG PS of 0 to 2/3). Patients received either a VELCADE-containing induction regimen (n=787) or a non-VELCADE-containing induction regimen (n=785). These studies evaluated VELCADE in combination with: 1) dexamethasone and adriamycin (MMY- 3003), 2) thalidomide and dexamethasone (MMY-3010), or 3) dexamethasone alone (IFM-2005- 01). VELCADE-containing induction regimens were compared to regimens including vincristine, adriamycin and dexamethasone or thalidomide and dexamethasone.

The VELCADE-based treatment group had improved PFS and TTP compared with the non- VELCADE-based treatment group. In addition, patients who received a VELCADE-containing induction regimen had improved post-transplant and post induction response rates compared to those who received a non-VELCADE-containing induction regimen.

Integrated efficacy results from studies MMY-3003, IFM-2005-01, MMY-3010 are summarized in the following table:

Table 10: Summary of integrated efficacy of VELCADE (Vc)-based induction therapy in previously untreated multiple myeloma patients eligible for autologous stem cell transplantation

Efficacy Endpoint	Vc-containing induction therapy n=787	Non-Vc-containing induction therapy n=785
Progression-free survival		
Number assessed	787	785
Events[a] n (%)	388 (49.3)	453 (57.7)
Median (months)[a] (95% CI)	35.9 (32.8, 39.2)	28.6 (26.4, 31.7)
Hazard ratio[b](95% CI)	0.75 (0.65, 0.85)	
p-value[c]	< 0.0001	
Response Rate (Post Transplant)		
Number assessed	775	772
CR n (%)	199 (26)	106 (14)
nCR n(%)	99 (13)	76 (10)
CR + nCR n (%)	298 (38)	182 (24)
Odds ratio[d](95% CI)	2.05 (1.64, 2.56)	
p-value[e]	<0.0001	
VGPR n(%)	165 (21)	133 (17)
PR n(%)	152 (20)	211(27)
Overall response rate (CR+nCR+VGPR+PR) n(%)	615(79)	526(68)
Odds ratio[d](95% CI)	1.81 (1.43, 2.27)	
p-value[e]	<0.0001	
Response Rate (Post Induction)		
Number assessed	775	772
CR n (%)	105(14)	32 (4)
nCR n(%)	70 (9)	31 (4)
CR + nCR n (%)	175 (23)	63 (8)
Odds ratio[d](95% CI)	3.45 (2.52, 4.72)	
p-value[e]	<0.0001	
VGPR n(%)	187 (24)	76(10)
PR n(%)	284 (37)	341(44)
Overall response rate (CR+nCR+VGPR+PR) n(%)	646(83)	480(62)
Odds ratio[d](95% CI)	3.05 (2.40, 3.87)	
p-value[e]	<0.0001	
Time to Progression		
Number assessed	787	785
Events[a] n (%)	368 (46.8)	428 (54.5)
Median (months)[a](95% CI)	37.5 (35.3, 39.9)	31.3 (28.2, 33.4)
Hazard ratio[b](95% CI)	0.76 (066, 088)	
p-value[c]	0.0001	
Overall Survival		
Number assessed	787	785
Events[a] (deaths) n (%)	175 (22.2)	207 (26.4)
3-year survival rate[a](%) (95% CI)	79.7(76.4, 82.5)	74.4(70.9, 77.5)
Hazard ratio[b](95% CI)	0.81 (0.66, 0.99)	
p-value[c]	0.0402	

Note: Median follow-up duration 37 months

CI=confidence interval; CR=complete response; nCR=near complete response; VGPR= very good partial response; PR=partial response. Note: VGPR is not reported as a response category for Study MMY-3010.

[a] Based on Kaplan-Meier product limit estimates.

[b] Hazard ratio estimate is based on Cox model stratified by study. A hazard ratio less than 1 favors the Vc-containing induction therapy.

[c] Log-rank test stratified by study.

[d] Cochran-Mantel-Haenszel estimate stratified by study. An odds ratio greater than 1 favors the Vc-containing induction therapy.

[e] P-value from the Cochran Mantel-Haenszel chi-squared test.

A fourth phase 3 randomized, open-label, multicenter trial (MMY-3006) was conducted in 480 patients (men and women aged 18 to 65 years of age with previously untreated multiple myeloma). In this study, VELCADE-containing induction regimens were

compared to regimens containing thalidomide and dexamethasone. The results of this study were consistent with those of the integrated analysis demonstrating improved post–induction CR+nCR rates (31% versus 11% ; p<0.0001), post-transplant CR+nCR rates (55% versus 41%; p=0.0025), and a 37% reduction in the risk of disease progression or death (HR = 0.63 [95% CI: 0.45, 0.88]; p=0.0061) with the VELCADE-based induction regimen as compared with its non-VELCADE based comparator regimen. The safety profile in the VELCADE-containing regimen was consistent with the known safety profile of VELCADE.

A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma After Prior Therapy

The safety and efficacy of Velcade in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study [M34103-053 (PINNACLE)] of 155 patients with progressive disease who had received at least 1 prior therapy. Velcade was administered at the recommended dose of 1.3 mg/m^2. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to Velcade are described in Table 11.

Table 11: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study (PINNACLE)

[a]Response Analyses (N = 141)	N (%)	95% CI
Overall Response Rate (IWRC) (CR + Cru + PR)	47 (33)	(26, 42)
Complete Response (CR + CRu)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (26)	(19, 34)
Time to Event Analyses	Median	95% CI
Kaplan-Meier Estimated Duration of Response		
CR + CRu + PR (N = 47)	9.2 months	(4.9, 13.5)
CR + CRu (N = 11)	13.5 months	(13.5, NE)
Kaplan-Meier Estimated Time to Progression (N = 155)	6.2 months	(4.0, 6.9)
** Kaplan-Meier Estimated Treatment Free Interval, CR + CRu (N = 11)	13.8 months	(13.4, NE)
Median Time to Next Treatment		
CR + CRu + PR (N = 47)	12.7 months	(9.33, NE)
CR + CRu (N = 11)	19.4 months	(17.8, NE)

*Based on International Response Workshop Criteria (IRWC).
Cru = Complete Response unconfirmed
NE=not estimable**Additional analyses

With a median duration of follow-up of more than 13 months in surviving patients, the median survival had not yet been reached and the Kaplan-Meier estimate of 1-year survival was 69%.
The Kaplan-Meier estimate of 1-year survival was 94% in responders and 100% in those achieving CR or CRu.

Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (LYM-3002) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) to determine whether VELCADE administered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) resulted in improvement in progression free survival (PFS) when compared to the combination of of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This clinical study utilized independent pathology confirmation and independent radiologic response assessment.
Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m2) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12-21); rituximab (375 mg/m2) on Day 1; cyclophosphamide (750 mg/m2) on Day 1; doxorubicin (50 mg/m2) on Day 1; and prednisone (100 mg/m2) on Day 1 through Day 5 of the 21-day treatment cycle. For patients with a response first documented at Cycle 6, two additional treatment cycles were given.
Median patient age was 66 years, 74% were male, 66% were Caucasian and 32% were 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 (high-intermediate) and 74% had Stage IV disease. Median number of cycles received by patients in both treatment arms was 6 with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to 2 additional cycles. The majority of the patients in both groups received 6 or more cycles of treatment, 83% in the R-CHOP group and 84% in the VcR-CAP group.
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 response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC).

A statistically significant benefit in favor of the VcR-CAP treatment group was observed for PFS, TTP, TNT, TFI overall complete response rate, and overall survival. At a median follow-up of 40 months, a 59% improvement in the primary endpoint of PFS (Hazard Ratio [HR]=0.63; p < 0.001) was observed in the Vc-RCAP group (median=24.7 months) as compared to the RCHOP group (median=14.4 months). The median duration of complete response was more than double in the VcR-CAP group (42.1 months) compared with the R-CHOP group (18 months) and the duration of overall response was 21.4 months longer in the VcR-CAP group. At a median follow-up of 40 months, median OS (56.3 months in the R-CHOP group, and not reached in the VcR-CAP group) favored the VcR-CAP group, (estimated HR=0.80; p=0.173). There was a trend towards prolonged overall survival favoring the VcR-CAP group; the estimated 4-year survival rate was 53.9% in the R-CHOP group and 64.4% in the VcR-CAP group.
The final analysis for OS was performed after a median follow-up of 82 months. Median OS in the VR-CAP group was 90.7 months, almost three years more than the OS achieved in the R-CHOP group, which was 55.7 months (HR=0.66; p=0.001).
Efficacy results are presented in Table 12

Table 12: Summary of Efficacy Outcomes in a Phase 3 Mantle Cell Lymphoma Study in Previously Untreated Patients (LYM-3002)

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7)	165 (67.6)	HR[d](95% CI)=0.63 (0.50;0.79)
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	p-value[e] < 0.001
Progression free survival (Investigator)[b]			
Events n (%)	128 (52.7)	179 (73.4)	HR[d](95% CI)=0.51 (0.41; 0.65)
Median[c] (95% CI) (months)	30.7 (25.1; 37.3)	16.1 (14.0; 18.4)	p-value[e] < 0.001
Time to Progression[a]			
Events n (%)	114 (46.9)	148 (60.7)	HR[d](95% CI)=0.58 (0.45;0.74)
Median[c](95% CI) (months)	30.5 (22.9; 40.9)	16.1(13.7;18.1)	p-value[e] < 0.001
Time to Next Anti-lymphoma Therapy			
Events n (%)	94 (38.7)	145 (59.4)	HR[d] (95% CI)=0.50 (0.38;0.65)
Median[c] (95% CI) (months)	44.5 (38.8; NE)	24.8 (22.1; 27.5)	p-value[e] < 0.001
Treatment Free Interval			
n: All Treated Patients	240	242	
Events n (%)	93 (38.8)	145 (59.9)	HR[d] (95% CI)=0.50 (0.38; 0.65)
Median[c] (95% CI) (months)	40.6 (33.6; NE)	20.5 (17.8; 22.8)	p-value[e] < 0.001
Overall survival at median follow up of 82 months			
n: ITT patients	243	244	
Events n (%)	103 (42.4)	138 (56.6)	HR[d] (95% CI)=0.66 (0.51; 0.85)
Median[c] (95% CI) (months)	90.7 (71.4; NE)	55.7 (47.2; 68.9)	p-value[e] =0.001
Response Rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[h] n(%)	122 (53.3)	95(41.7)	OR[f](95% CI)=1.688 (1.148; 2.481) p-value[g] =0.007
Overall radiological response (CR+CRu+PR)[i] n(%)	211 (92.1)	204 (89.5)	OR[f](95% CI)=1.428 (0.749; 2.722) p-value[g] =0.275
Response Duration			
Duration of complete response (CR+CRu)[j]			
n = response-evaluable patients	122	95	
Median[c] (95% CI) (months)	42.1 (30.7; 49.1)	18.0 (14.0; 23.4)	
Duration of Response (CR+CRu+PR)[k]			
n: response-evaluable subjects	211	204	
Median[c] (95% CI) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

[a] Based on IRC assessment (radiological data only).
[b] Based on Investigator assessment.
[c] Based on Kaplan-Meier product limit estimates.
[d] 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 VcR-CAP.
[e] Based on Log rank test stratified with IPI risk and stage of disease.
[f] 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 VcR-CAP.
[g] P-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.
[h] Include all CR + CRu, by IRC, bone marrow and LDH.
[i] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
[j] Calculated from first date of complete response (CR+CRu by IRC, bone marrow and LDH) to date of PD or death due to PD.
[k] Calculated from first date of response (include all radiological CR+CRu+PR by IRC) to date of PD or death due to PD.
IRC=Independent Review Committee; IPI=International Prognostic Index; LDH = Lactate dehydrogenase;
CR=Complete Response; CRu= Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval,
HR=hazard ratio; OR= odds ratio; ITT= intent to treat; PD=Progressive disease

Patients with Previously Treated Light-Chain (AL) Amyloidosis
A Phase 1/2 study was conducted to determine the safety and efficacy of VELCADE in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular VELCADE did not exacerbate target organ damage (heart, kidney and liver). In 49 evaluable patients treated at 1.6 mg/m^2 weekly or 1.3 mg/m^2 twice weekly, a 67.3% response rate (including a 28.6% CR rate) as measured by haematological response (M- protein) was reported. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Pediatric Use
The safety and effectiveness of Velcade in children has not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving Velcade; in the patients studied with multiple myeloma and mantle cell lymphoma, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic Properties
Pharmacokinetics
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma, 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 106ng/mL for the 1.0mg/m^2 dose and 89 to 120ng/mL for the 1.3mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0mg/m^2 and 1.3mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0mg/m^2 and 1.3mg/m^2, respectively.

In the PK/PD substudy in Phase 3 trial, following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m2 dose to multiple myeloma patients (n = 14 for IV, n = 17 for SC), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for SC and IV administration. The C_{max} after SC administration (20.4 ng/mL) was lower than IV (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 of bortezomib ranged from 489 to 1884L/m^2 single- or repeat dose IV administration of 1.0mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.

Metabolism
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. 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.

Pooled plasma data from 8 patients at 10 min and 30 min after IV dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination
The pathways of elimination of bortezomib have not been characterized in humans.

Special Populations
Age, Gender, and Race
The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m2 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/m2, volume of distribution at steady-state was 834 (39%) L/m2, 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.
The effects of gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in 60 cancer patients 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-normalized bortezomib 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 monitored closely (see table 18).

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-normalized AUC and C_{max}) was comparable among all the groups (see *Posology and Method of Administration*).

Pediatric
There are no pharmacokinetic data in pediatric patients.

PRECLINICAL SAFETY DATA
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with bortezomib.
Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2. Velcade could have a potential effect on either male or female fertility.

INDICATIONS
Multiple myeloma:
Velcade (bortezomib) in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.
VELCADE in combination with other medicinal products (refer to Posology section for Previously Untreated Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation), is indicated for the treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
Velcade (bortezomib) for Injection is indicated for the treatment of multiple myeloma patients who have received at least 1 prior therapy and have demonstrated disease progression on the last therapy given as alone or in combination with Pegylated lyposomal-doxorubicin.

Mantle Cell Lymphoma:
Velcade (bortezomib) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone is indicated for the treatment of patients with previously untreated mantle cell lymphoma.
Velcade (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

POSOLOGY AND METHOD OF ADMINISTRATION
Velcade 1mg:
Velcade may be administered intravenously (at a concentration of 1 mg/mL) as a 3 to 5 second bolus injection

Velcade 3.5mg:
Velcade may be administered:
- Intravenously (at a concentration of 1 mg/mL) as a 3 to 5 second bolus injection or
- Subcutaneously (at a concentration of 2.5 mg/mL)

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

At least 72 hours should elapse between consecutive doses of Velcade.

VELCADE IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY. Intrathecal administration has resulted in death.

VELCADE retreatment may be considered for multiple myeloma patients who had previously responded to treatment with VELCADE (see below and *Pharmacodynamic properties*).

Monotherapy
Relapsed Multiple Myeloma and relapsed Mantle Cell Lymphoma.
Recommended Dosage
The recommended dose of Velcade is 1.3 mg/m^2/dose administered twice weekly for 2 weeks (Days, 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of Velcade.
It is recommended that patients with a confirmed complete response receive 2 additional cycles of Velcade beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of Velcade therapy.

Dose Modification and Reinitiation of Therapy
Velcade therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see *Special Warnings and Special Precautions for Use*). Once the symptoms of the toxicity have resolved, Velcade therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience Velcade-related neuropathic pain and/or peripheral sensory neuropathy (Table 13). Patients with pre-existing severe neuropathy should be treated with Velcade only after careful risk/benefit assessment.

Table 13: Recommended Dose Modification for Velcade-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce Velcade to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold Velcade therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of Velcade at 0.7 mg/m^2 and change treatment schedule to once per week
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue Velcade

NCI Common Toxicity Criteria

Administration

Velcade 1mg:

Velcade is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection.

Velcade 3.5mg:

Velcade is administered intravenously or subcutaneously. When administered intravenously, Velcade is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection. For subcutaneous administration, the reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local injection site reactions occur following Velcade injection subcutaneously, a less concentrated Velcade solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously, or changed to IV injection.

Combination Therapy

Previously Untreated Multiple Myeloma - Patients who are Not Eligible for Stem Cell Transplantation

Recommended Dosage in Combination with Melphalan and Prednisone

Velcade (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 14. In Cycles 1-4, Velcade is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Velcade is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of Velcade.

Table 14: Recommended Dosage Regimen for Velcade when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma who are not eligible for stem cell transplantation

Twice Weekly Velcade (Cycles 1-4)												
Week	1				2		3	4		5		6
Vc (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 Velcade (Cycles 5-9)									
Week	1				2	3	4	5	6
Vc (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

Vc = Velcade; M = melphalan, P = prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone

Dose modification and re-initiation of therapy when Velcade is administered in combination with melphalan and prednisone.

Prior to initiating a new cycle of therapy:

- Platelet count should be $\geq 70 \times 10^9$/L and the absolute neutrophil count (ANC) should be $\geq 1.0 \times 10^9$/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 15: Dose Modifications During Subsequent Cycles:

Toxicity	**Dose modification or delay**
Hematological toxicity during a cycle: • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
• If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.75 \times 10^9$/L on a Velcade dosing day (other than day 1)	Velcade dose should be withheld.
• If several Velcade doses in a cycle are withheld (> 3 doses during twice weekly administration or $\geq$ 2 doses during weekly administration)	Velcade 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-hematological toxicities	Velcade therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Velcade 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 Velcade-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Velcade as outlined in Table 13.

For additional information concerning melphalan and prednisone, see manufacturer's prescribing information.

Previously Untreated Multiple Myeloma – Patients who are Eligible for Stem Cell Transplantation

Recommended Dosage

Combination therapy with dexamethasone

VELCADE 1mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3mg/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 VELCADE. Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10, and 11 of the VELCADE treatment cycle. Four treatment cycles of this combination therapy are administered.

Table 16: Posology for VELCADE combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

Vc + Dx	**Cyles 1 to 4**			
	Week	**1**	**2**	**3**
	Vc (1.3mg/m^2)	Day 1,4	Day 8, 11	Rest period
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-

Vc = VELCADE; Dx= dexamethasone

For VELCADE dosage adjustment for transplant eligible patients follow dose modification guidelines described under monotherapy above.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal-Doxorubicin

For VELCADE dosage and dose modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the VELCADE 3 week regimen as a 1 hour intravenous infusion administered after the VELCADE injection.

For additional information concerning pegylated liposomal-doxorubicin, see manufacturer's prescribing information.

Previously Untreated Mantle Cell Lymphoma

Recommended Dosage in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

For VELCADE dosage, see Monotherapy. Six VELCADE cycles are administered. For patients with a response first documented at Cycle 6, two additional VELCADE cycles are recommended.

The following medicinal products are administered on Day 1 of each VELCADE 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 treatment cycle.

Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L
- Hemoglobin should be ≥ 8 g/dL (≥ 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

VELCADE treatment must be withheld at the onset of any Grade 3 non-hematological or Grade 3 hematological toxicities, excluding neuropathy (see *Special Warnings and Special Precautions for Use*). For dose adjustments, see Table below.

Table 17: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Toxicity	**Posology modification or delay**
Hematological toxicity	VELCADE therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0.75 x 10^9/L and a platelet count ≥ 25 x 10^9/L.

• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x 10^9/L	• If, after VELCADE has been held, the toxicity does not resolve, as defined above, then VELCADE must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 0.75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, VELCADE 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)
• If platelet counts < 25 x 10^9/L. or ANC < 0.75 x 10^9/L on a VELCADE dosing day (other than Day 1)	VELCADE dose should be withheld
Grade ≥ 3 non-hematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 13.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see manufacturer's prescribing information.

Special Populations

Patients with Renal Impairment

The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency with creatinine clearance ≥ 20 mL/min. Since dialysis may reduce VELCADE concentrations, the drug should be administered after the dialysis procedure (see *Pharmacokinetic properties*).

Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. For patients with moderate or severe hepatic impairment, see Table 18 below, (also, see *Pharmacokinetic properties*):

Table 18: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose in Multiple Myeloma and Relapsed Mantle Cell Lymphoma (1.3 mg/m^2 twice weekly)**
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x - 1.5x ULN	Any	None
Moderate	> 1.5x - 3x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first 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	> 3x ULN	Any	

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Velcade should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

There have been fatal cases of inadvertent intrathecal administration of Velcade. Velcade is for IV and subcutaneous use only**. DO NOT ADMINISTER VELCADE INTRATHECALLY.**

Peripheral Neuropathy

Velcade treatment causes a peripheral neuropathy (PN) that is predominantly sensory.
However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported.

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with Velcade. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 study comparing Velcade IV vs SC the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for SC and 41% for IV (p=0.0124). Grade ≥ 3 peripheral neuropathy occurred in 6% of subjects in the SC treatment group, compared with 16% in the IV treatment group (p=0.0264) **(Table 11).** Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting Velcade subcutaneously.

Patients experiencing new or worsening peripheral neuropathy may require a change in the dose and schedule of Velcade (see Posology and Method of Administration). Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of Velcade vs dexamethasone. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension

In phase 2 and 3 single agent multiple myeloma studies, the incidence of hypotension (postural, orthostatic, and Hypotension Not Otherwise Specified) was 11% to 12%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids and/or sympathomimetics *(see Undesirable Effects).*

Cardiac Disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the single agent phase 3 multiple myeloma study of Velcade vs dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% respectively. The incidence of heart failure events (acute pulmonary oedema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary oedema) was similar in the Velcade and dexamethasone groups, 5% and 4%, respectively.
There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Hepatic Events

Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of Velcade. There is limited re-challenge information in these patients.

Pulmonary Disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving Velcade. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

In a clinical trial, two patients given high-dose cytarabine (2g/m^2 per day) by continuous infusion with daunorubicin and Velcade for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2g/m^2 per day) by continuous infusion over 24 hours is not recommended.

There have been reports of pulmonary hypertension associated with Velcade administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, a prompt comprehensive diagnostic evaluation should be conducted.

Patients with Renal Impairment

No clinical information is available on the use of Velcade in patients with creatinine clearance values less than 13 mL/min and patients on hemodialysis. These patients should be closely monitored for toxicities when treated with Velcade.

Laboratory Tests

Complete blood counts (CBC) should be frequently monitored throughout treatment with Velcade.

Thrombocytopenia/Neutropenia

Velcade is associated with thrombocytopenia and neutropenia (see *Undesirable Effects*). Platelets were lowest at Day 11 of each cycle of Velcade treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease and recovery remain in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied. Platelet counts should be monitored prior to each dose of Velcade. Velcade therapy should be held when the platelet count is <25,000/uL and reinitiated at a reduced dose (see *Posology*

and Method of Administration and *Undesirable Effects*). There have been reports of gastrointestinal and intracerebral hemorrhage in association with Velcade. Transfusion may be considered.
In the single-agent multiple myeloma study of VELCADE vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in Table 19. The incidence of significant bleeding events (≥ Grade 3) was similar on both the Velcade (4%) and dexamethasone (5%) arms.

Table 19: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Single Agent Phase 3 Multiple Myeloma Study of Velcade vs Dexamethasone

Pretreatment Platelet Count[a]	Number of Patients (N=331)[b]	Number (%) of Patients with Platelet Count <10,000/µL	Number (%) of Patients with Platelet Count 10,000-25,000/µL
≥75,000/µL	309	8 (3%)	36 (12%)
≥50,000/µL-<75,000/µL	14	2 (14%)	11 (79%)
≥10,000/µL-<50,000/µL	7	1 (14%)	5 (71%)

[a] A baseline platelet count of 50,000/µL was required for study eligibility.
[b] Data were missing at baseline for 1 patient.

In the combination study of VELCADE with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was 32% versus 2% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ Grade 3) was 1.7% (4 patients) in the VcR-CAP arm and was 1.2% (3 patients) in the R-CHOP arm.
There were no deaths due to bleeding events in either arm. There were no CNS bleeding events in the VcR-CAP arm; there was 1 bleeding event in the R-CHOP arm. Platelet transfusions were given to 23% of the patients in the VcR-CAP arm and 3% of the patients in the R-CHOP arm.
The incidence of neutropenia (≥ Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥ Grade 4) was 5% in the VcR-CAP arm and was 6% in the R-CHOP arm. Colony-stimulating factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

Gastrointestinal Adverse Events
Velcade treatment can cause nausea, diarrhea, constipation, and vomiting (see Undesirable Effects) sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving Velcade therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

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

Patients with Hepatic Impairment
Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with Velcade at reduced starting doses and closely monitored for toxicities. (See *Posology and Method of Administration and Pharmacokinetics properties*)

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of PRES in patients receiving Velcade. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue Velcade. The safety of reinitiating Velcade therapy in patients previously experiencing PRES is not known.

Thrombotic Microangiopathy
Cases sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received VELCADE. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop VELCADE and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing TTP/HUS is not known.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with VELCADE, 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 VELCADE. 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 VELCADE. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELCADE. 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 VELCADE if PML is diagnosed.

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.

UNDESIRABLE EFFECTS

Summary of Clinical Trials of Velcade IV in Patients with Relapsed/Refractory Multiple Myeloma:

The safety and efficacy of Velcade were evaluated in 3 studies at the recommended dose of 1.3 mg/m^2. These included a phase 3 randomized, comparative study, versus dexamethasone of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy (M34101-039); a phase 2 single arm, open-label, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy (M34100-025); and a phase 2 dose-response clinical study in relapsed multiple myeloma for patients who had progressed or relapsed on or after first line therapy with Velcade 1.0 mg/m^2 or 1.3 mg/m^2 (M34100-024).

Table 20: Velcade Adverse Drug Reactions in Phase 2 and Phase 3 Relapsed/Refractory Multiple Myeloma Studies

MedDRA System Organ Class **Preferred term**	**Study No.**	
	M34101-039 (N=331)	M34100-024 / M34100-025 (N=228[†])
Blood and lymphatic system disorders		
Thrombocytopenia	115 (35%)	97 (43%)
Anemia	87 (26%)	74 (32%)
Neutropenia	62 (19%)	55 (24%)
Leucopenia	24 (7%)	15 (7%)
Lymphopenia	15 (5%)	11 (5%)
Pancytopenia	2 (<1%)	6 (3%)
Febrile Neutropenia	1 (<1%)	1 (<1%)
Cardiac disorders		
Arrhythmias	4 (1%)	2 (<1%)
Tachycardia	9 (3%)	17 (7%)
Atrial Fibrillation	6 (2%)	2 (<1%)
Palpitations	5 (2%)	4 (2%)
Acute Development or exacerbation of cardiac failure, including CHF	7 (2%)	8 (4%)
Pulmonary edema	6 (2%)	3 (1%)
*Cardiogenic shock**	1 (<1%)	-
New onset of decreased left ventricular ejection fraction	1 (<1%)	-
Atrial Flutter	1 (<1%)	-
Bradycardia	3 (<1%)	1(<1%)
Ear & labyrinth disorders		
Hearing Impairment	1 (<1%)	1 (<1%)
Eye disorders		
Blurred Vision	9 (3%)	25 (11%)
Conjunctival infection and irritation	14 (4%)	7 (3%)
Gastrointestinal (GI) disorders		

Constipation	140 (42%)	97 (43%)
Diarrhea	190 (57%)	116 (51%)
Nausea	190 (57%)	145 (64%)
Vomiting	117 (35%)	82 (36%)
Gastrointestinal and abdominal pain, excluding oral and throat	80 (24%)	48 (21%)
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (<1%)
Eructation	2 (<1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
*GI hemorrhage (upper and lower GI tract) **	7 (2%)	3 (1%)
Rectal hemorrhage (includes hemorrhagic diarrhea)	7 (2%)	3 (1%)
Tongue ulceration	2 (<1%)	1 (<1%)
Retching	3 (<1%)	2 (<1%)
Upper GI hemorrhage	1 (<1%)	-
Hematemesis	1 (<1%)	-
Oral mucosal petechiae	3 (<1%)	-
Ileus Paralytic	1 (<1%)	2 (<1%)
General disorders and administration site conditions		
Asthenic conditions	201 (61%)	149 (65%)
Weakness	40 (12%)	44 (19%)
Fatigue	140 (42%)	118 (52%)
Lethargy	12 (4%)	9 (4%)
Malaise	13 (4%)	22 (10%)
Pyrexia	116 (35%)	82 (36%)
Rigors	37 (11%)	27 (12%)
Oedema of the lower limbs	35 (11%)	27 (12%)
Neuralgia	21 (6%)	5 (2%)
Chest Pain	26 (8%)	16 (7%)
Injection site pain and irritation	1 (<1%)	1 (<1%)
Injection site phlebitis	1 (<1%)	1 (<1%)
Hepatobiliary disorders		
Hyperbilirubinemia	1 (<1%)	-
Abnormal liver function tests	3 (<1%)	2 (<1%)
Hepatitis	2 (<1%) in study M34101-040‡	-
Immune system disorders		
Drug hypersensitivity	1 (<1%)	1 (<1%)
Infections and infestations		
Upper respiratory tract infection	26 (8%)	41 (18%)
Nasopharyngitis	45 (14%)	17 (7%)
Lower respiratory tract and lung infections	48 (15%)	29 (13%)
*Pneumonia**	21 (6%)	23 (10%)
Herpes zoster (including multidermatomal or disseminated)	42 (13%)	26 (11%)
Herpes simplex	25 (8%)	13 (6%)
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (<1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (<1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
*Sepsis and bacteremia**	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-

Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		
Increased ALT	3 (<1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (<1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%	18 (8%)
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)		
Tumor Lysis Syndrome	*2 (<1%) in study M34101-040*[‡]	-
Nervous system disorders		
Peripheral neuropathy[§]	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91 (27%)	53 (23%)
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (<1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (<1%)	-
Ageusia	2 (<1%)	-
Psychiatric disorders		
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal Impairment and Failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnea	65 (20%)	50 (22%)
Exertional dyspnea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhea	4 (1%)	14 (6%)
Hemoptysis	3 (<1%)	2 (<1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petechiae	6 (2%)	7 (3%)
*Cerebral hemorrhage**	1 (<1%)	-

[†]All 228 patients received Velcade at a dose of 1.3 mg/m^2

*Includes fatal outcome

‡A study of Velcade at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101-039
§Including all preferred terms under the MedDRA HLT "peripheral neuropathy NEC"

Summary of Clinical Trials of Velcade *IV vs SC in patients with relapsed multiple myeloma:*
The safety and efficacy of Velcade SC were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of Velcade IV vs SC in 222 patients with relapsed multiple myeloma.

Table 21: Incidence of Velcade Adverse Drug Reactions reported in ≥ 10% of patients in the Phase 3 Relapsed Multiple Myeloma Study comparing Velcade IV and SC

	IV (N=74)			**SC (N=147)**		
MedDRA System Organ Class	**Total**	**Toxicity Grade, n (%)**		**Total**	**Toxicity Grade, n (%)**	
Preferred Term	**n (%)**	**3**	**≥ 4**	**n (%)**	**3**	**≥ 4**
Blood and lymphatic system disorders						
Anaemia	26 (35)	6 (8)	0	53 (36)	14 (10)	4 (3)
Leukopenia	16 (22)	4 (5)	1 (1)	29 (20)	9 (6)	0
Neutropenia	20 (27)	10 (14)	3 (4)	42 (29)	22 (15)	4 (3)
Thrombocytopenia	27 (36)	8 (11)	6 (8)	52 (35)	12 (8)	7 (5)
Gastrointestinal disorders						
Abdominal pain	8 (11)	0	0	5 (3)	1 (1)	0
Abdominal pain upper	8 (11)	0	0	3 (2)	0	0
Constipation	11 (15)	1 (1)	0	21 (14)	1 (1)	0
Diarrhoea	27 (36)	3 (4)	1 (1)	35 (24)	2 (1)	1 (1)
Nausea	14 (19)	0	0	27 (18)	0	0
Vomiting	12 (16)	0	1 (1)	17 (12)	3 (2)	0
General disorders and administration site conditions						
Asthenia	14 (19)	4 (5)	0	23 (16)	3 (2)	0
Fatigue	15 (20)	3 (4)	0	17 (12)	3 (2)	0
Pyrexia	12 (16)	0	0	28 (19)	0	0
Infections and infestations						
Herpes zoster	7 (9)	1 (1)	0	16 (11)	2 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	7 (9)	0	0	14 (10)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	8 (11)	2 (3)	0	8 (5)	1 (1)	0
Nervous system disorders						
Headache	8 (11)	0	0	5 (3)	0	0
Neuralgia	17 (23)	7 (9)	0	35 (24)	5 (3)	0
Peripheral sensory neuropathy	36 (49)	10 (14)	1 (1)	51 (35)	7 (5)	0
Psychiatry disorders						
Insomnia	8 (11)	0	0	18 (12)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	9 (12)	2 (3)	0	11 (7)	2 (1)	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator. Percentages of toxicity grade sub-groups calculated with the number of subjects in each group as denominator.

Although, in general safety data were similar for the IV and SC treatment groups, the following table highlights differences larger than 10% in the overall incidence of adverse drug reactions between the two treatment arms.

Table 22: Incidence of Adverse Drug Reactions with >10% Difference in Overall Incidence between Treatment Arms in the Phase 3 Relapsed Multiple Myeloma Study comparing Velcade IV and SC, by Toxicity Grade and Discontinuation

	IV (N=74)			**SC (N=147)**		
MedDRA System Organ Class	**Category n (%)**			**Category n (%)**		
MedDRA High Level Term	**TEAE**	**G ≥ 3**	**Disc**	**TEAE**	**G ≥ 3**	**Disc**
All subjects with TEAE	73 (99)	52 (70)	20 (27)	140 (95)	84 (57)	69 (22)
Gastrointestinal disorders						
Diarrhoea (excl infective)	27 (36)	4 (5)	1 (1)	35 (24)	3 (2)	1 (1)
Gastrointestinal and abdominal pains (excl oral and throat)	14 (19)	0	0	9 (6)	1 (1)	0
General disorders and administration site conditions						
Asthenic conditions	29 (39)	7 (9)	1 (1)	40 (27)	6 (4)	2 (1)
Infections and infestations				20 (14)		
Upper respiratory tract infections	19 (26)	2 (3)	0		0	0
Nervous system disorders				56 (38)		
Peripheral neuropathy[a]	39 (53)	12 (16)	10 (14)		9 (6)	9 (6)

[a] Represents the high-level term
TEAE = Treatment- Emergent Adverse Event; G ≥ 3 = Toxicity Grade greater than equal to 3
Disc = Discontinuation of any study drug

Patients who received Velcade subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment-emergent adverse drug reactions that were grade 3 or higher in toxicity (57% vs 70% respectively), and a 5% lower incidence of discontinuation of Velcade (22% vs 27%). The overall incidence of diarrhea (24% for the SC arm vs 36% for the IV arm), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm) and peripheral neuropathy NEC (38% SC arm vs 53% IV arm) were 12%-15% lower in the subcutaneous group than the intravenous group. In addition, the incidence of peripheral neuropathies that were grade 3 or higher in toxicity was 10 % lower (6% for SC vs 16% for IV), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (14%).

Six percent of patients were reported to have had an adverse local reaction to SC administration, mostly redness. Only 2 (1%) subjects were reported as having severe reactions. These severe local reactions were 1 case of pruritus and 1 case of redness. These reactions seldom led to dose modifications and all resolved in a median of 6 days.

VELCADE Retreatment in Relapsed Multiple Myeloma
The following table describes adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received retreatment with VELCADE IV (Study MMY-2036).

Table 23: Incidence of VELCADE Adverse Drug Reactions reported in ≥ 10% of patients (Study MMY-2036)

	Vc Retreatment (MMY-2036)		
		Toxicity Grade	
	Total	3	≥4
Analysis Set: Safety, N	130		
Total no. subjects with adverse drug reactions, n (%)	126 (97)		
MedDRA system organ class			
Preferred term			
Blood and lymphatic system disorders			
Thrombocytopenia	71 (55)	19 (15)	14 (11)

Anaemia	48 (37)	5 (4)	1 (1)
Neutropenia	23 (18)	9 (7)	0
Leukopenia	20 (15)	5 (4)	0
Gastrointestinal disorders			
Diarrhoea	45 (35)	9 (7)	0
Constipation	36 (28)	0	0
Nausea	14 (11)	0	0
General disorders and administration site conditions			
Pyrexia	31 (24)	2 (2)	0
Asthenia	29 (22)	6 (5)	0
Fatigue	21 (16)	0	0
Oedema peripheral	15 (12)	0	0
Infections and infestations			
Respiratory tract infection	17 (13)	3 (2)	1 (1)
Bronchitis	13 (10)	1 (1)	0
Nervous system disorders			
Peripheral sensory neuropathy	22 (17)	4 (3)	0
Neuropathy peripheral	13 (10)	3 (2)	0
Respiratory, thoracic and mediastinal disorders			
Cough	15 (12)	1 (1)	0
Dyspnoea	14 (11)	1 (1)	0

Key: Vc = VELCADE; AE = Adverse event; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events
Note: Percentages are calculated with the number of subjects in each group as denominator.
Adverse events are reported using MedDRA version 14.1.
In Study MMY-2036, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.
AEs with missing toxicity grade are assigned grade 3.

Summary of Clinical Trials of VELCADE Combination Therapy in Patients with Relapsed Multiple Myeloma
The following table describe adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received VELCADE in combination with pegylated liposomal doxorubicin (Study DOXIL-MMY-3001).

Table 24: Most Frequent (at Least 10 Percent in Any Treatment Group) Treatment emergent Adverse Drug Reactions by Toxicity Grade, System Organ Class and Preferred Term; Safety Analysis Set (Studies DOXIL-MMY-3001)

			Vc Combination Therapy	
	Vc Monotherapy		**Vc + DOXIL**	
	Total n (%)	**Grade ≥3 n (%)**	**Total n (%)**	**Grade ≥3 n (%)**
Analysis Set: Safety	318		318	
Total no. subjects with adverse drug reactions	301 (95)		314 (99)	
MedDRA system organ class				
Preferred term				
Gastrointestinal disorders				
Diarrhoea	124 (39)	16 (5)	145 (46)	23 (7)
Nausea	126 (40)	3 (1)	154 (48)	8 (3)
Constipation	98 (31)	2 (1)	99 (31)	3 (1)
Vomiting	69 (22)	3 (1)	101 (32)	13 (4)
Stomatitis	11 (3)	1 (< 1)	56 (18)	7 (2)
Abdominal pain	24 (8)	4 (1)	34 (11)	2 (1)
Nervous system disorders				
Peripheral neuropathy [a]	143 (45)	35 (11)	133 (42)	22 (7)
Neuralgia	63 (20)	14 (4)	54 (17)	9 (3)
Headache	56 (18)	0	59 (19)	3 (1)
Paraesthesia	31 (10)	0	41 (13)	1 (< 1)
Dizziness	26 (8)	4 (1)	32 (10)	4 (1)
General disorders and administration site conditions				

Fatigue	88 (28)	8 (3)	115 (36)	22 (7)
Pyrexia	71 (22)	4 (1)	100 (31)	4 (1)
Asthenia	56 (18)	12 (4)	71 (22)	19 (6)
Oedema peripheral	27 (8)	1 (< 1)	32 (10)	1 (< 1)
Blood and lymphatic system disorders				
Thrombocytopenia	89 (28)	53 (17)	106 (33)	76 (24)
Neutropenia	71 (22)	51 (16)	114 (36)	102 (32)
Anaemia	68 (21)	30 (9)	80 (25)	29 (9)
Infections and infestations				
Herpes zoster	29 (9)	6 (2)	34 (11)	6 (2)
Bronchitis	21 (7)	3 (1)	31 (10)	1 (< 1)
Upper respiratory tract infection	33 (10)	3 (1)	33 (10)	2 (1)
Musculoskeletal and connective tissue disorders				
Back pain	39 (12)	6 (2)	39 (12)	4 (1)
Pain in extremity	48 (15)	8 (3)	34 (11)	1 (< 1)
Arthralgia	27 (8)	5 (2)	34 (11)	1 (< 1)
Respiratory, thoracic and mediastinal disorders				
Cough	38 (12)	0	58 (18)	0
Dyspnoea	28 (9)	10 (3)	34 (11)	3 (1)
Metabolism and nutritional disorders				
Decreased appetite	50 (16)	1 (< 1)	83 (26)	8 (3)
Skin and subcutaneous tissue disorders				
Rash	29 (9)	3 (1)	48 (15)	2 (1)
Investigations				
Weight decreased	12 (4)	0	37 (12)	0
Psychiatric disorders				
Insomnia	43 (14)	2 (1)	35 (11)	0

Key: Vc = VELCADE; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events

[a] Includes the preferred terms of neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and polyneuropathy.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Adverse events are reported using MedDRA version 14.1.

In Study MMY-2045, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.

Summary of Clinical Trials in Patients with Previously Untreated Multiple Myeloma:

The following table describes safety data from 340 patients with previously untreated multiple myeloma who received Velcade IV (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective phase 3 study.

Table 25: Treatment-Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with Velcade IV in combination with melphalan and prednisone

		Vc-MP (n=340)			**MP (n=337)**	
MedDRA System Organ Class	**Total**	**Toxicity Grade, n (%)**		**Total**	**Toxicity Grade, n (%)**	
Preferred Term	**n (%)**	**3**	**≥ 4**	**N (%)**	**3**	**≥ 4**
Blood and lymphatic system disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anaemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhoea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal pain upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral Neuropathy	156 (46)	42 (12)	2 (1)	4 (1)	0	0

Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paraesthesia	42 (12)	6 (2)	0	4 (1)	0	0
General disorders and administration site conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and infestations						
Herpes zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and nutrition disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatry disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

Herpes zoster virus reactivation:
Physicians should consider using antiviral prophylaxis in patients being treated with Velcade. In the phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Summary of the Clinical Trial in Patients with Relapsed Mantle Cell Lymphoma
Safety data for patients with mantle cell lymphoma were evaluated in a phase 2 study [M34103-053 (PINNACLE)], which included 155 patients treated with Velcade at the recommended dose of 1.3 mg/m^2. The safety profile of Velcade in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritis were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Summary of Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma
Table 26 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received VELCADE (1.3 mg/m^2) administered IV in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.
The incidences of Grade ≥ 3 bleeding events were similar between the 2 arms (4 patients in the VcR-CAP arm and 3 patients in the R-CHOP arm). All of the Grade ≥ 3 bleeding events resolved without sequelae in the VcR-CAP arm.
Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the R-CHOP arm. Respiratory tract and lung infections were reported, with the predominant preferred term of pneumonia (VcR-CAP 8% versus R-CHOP 5%).
The incidence of herpes zoster reactivation was 4.6% in the VcR-CAP arm and 0.8% in the RCHOP arm. Antiviral prophylaxis was mandated by protocol amendment.

Table 26: Most Commonly Reported Adverse Reactions (≥ 5%) with Grades 3 and ≥ 4 Intensity in the Mantle Cell Lymphoma Study of VcR-CAP versus R-CHOP (N=482) (Study LYM-3002)

	VcR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and lymphatic system disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anaemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous system disorders						

Peripheral sensory neuropathy	53 (22)	11 (5)	1 (< 1)	45 (19)	6 (3)	0
Neuropathy peripheral	18 (8)	4 (2)	0	18 (7)	2 (1)	0
Hypoaesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paraesthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (< 1)	0	0
General disorders and administration site conditions						
Fatigue	43 (18)	11 (5)	1 (< 1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (< 1)	18 (7)	1 (< 1)	0
Oedema peripheral	16 (7)	1 (< 1)	0	13 (5)	0	0
Gastrointestinal disorders						
Nausea	54 (23)	1 (< 1)	0	28 (12)	0	0
Constipation	42 (18)	1 (< 1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (< 1)
Diarrhoea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (< 1)
Vomiting	24 (10)	1 (< 1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and subcutaneous tissue disorders						
Alopecia	31 (13)	1 (< 1)	1 (< 1)	33 (14)	4 (2)	0
Metabolism and nutrition disorders						
Hyperglycaemia	10 (4)	1 (< 1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (< 1)	0
Hypokalaemia	11 (5)	3 (1)	1 (< 1)	6 (2)	1 (< 1)	0
Vascular disorders						
Hypertension	15 (6)	1 (< 1)	0	3 (1)	0	0
Psychiatric disorders						
Insomnia	16 (7)	1 (< 1)	0	8 (3)	0	0

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Post-Marketing Experience

Clinically significant adverse drug reactions are listed here if they have not been reported above.

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with Velcade. The frequencies provided below reflect reporting rates and precise estimates of incidence cannot be made. These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥1/10), common (≥1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000, including isolated reports).

Table 27: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Thrombotic microangiopathy	Very Rare
Cardiac disorders	
Atrioventricular block complete, cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye disorders	
Ophthalmic herpes, optic neuropathy, blindness	Rare
Chalazion/blepharitis	Rare
Gastrointestinal disorders	
Ischemic colitis, acute pancreatitis	Rare
Intestinal obstruction	Uncommon
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy[a]	Very rare
Immune system disorders	

Angioedema	Rare
Anaphylactic reaction	Very Rare
Nervous system disorders	
Encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome	Rare
Guillain-Barré syndrome, demyelinating polyneuropathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease *Pulmonary hypertension*	Rare Rare
Skin and subcutaneous tissue disorders	
Stevens-Johnson Syndrome and toxic epidermal necrolysis *Acute febrile neutrophilic dermatosis (Sweet's syndrome)*	Very rare Rare

[a] Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE.

CONTRAINDICATIONS
Velcade is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.
Acute diffuse infiltrative pulmonary and pericardial disease.
VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of Velcade showed a mean bortezomib AUC reduction of 35% 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 inhibitor of CYP2C19, on the pharmacokinetics of Velcade 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 Velcade showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. The concomitant use of Velcade with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

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

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

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Drug Laboratory Test Interactions
None known.

Pregnancy and Lactation
Women of childbearing potential should avoid becoming pregnant while being treated with Velcade.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested {0.075 mg/kg (0.5 mg/m^2) in the rat and 0.05 mg/kg (0.6 mg/m^2) in the rabbit} when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If Velcade is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with Velcade.

Nursing Mothers
It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Velcade, women should be advised against breast feeding while being treated with Velcade.

Effects on Ability to Drive and Use Machines
Velcade may cause tiredness, dizziness, fainting, or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms.

Overdose
Cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

Overdosage more than twice the recommended dose in patients has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for Velcade overdosage. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see *Special Warnings* and *Special Precautions for Use* and *Posology and Method of Administration*).

PHARMACEUTICAL PARTICULARS
List of Excipients
Mannitol (E421)

Incompatibilities
This product must not be mixed with other medicinal products except those mentioned in Instructions for Use and Handing and Disposal.

Shelf Life
36 months
Unopened vials of Velcade are stable until the date indicated on the package when stored in the original package protected from light.

Special Precautions for Storage
Velcade contains no antimicrobial preservative. When reconstituted as directed, Velcade may be stored at 25°C (77°F). Reconstituted Velcade should be administered within 8 hours of preparation. The reconstituted material may be stored for up to 8 hours in the original vial or in a syringe. The total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

Do not store unopened vials above 30°C (86°F). Retain in original package to protect from light.

Keep out of reach of children.

Nature and Contents of Container

Five (5) or ten (10) mL, type 1, glass vial with a gray bromobutyl stopper and aluminum seal. The cap color of the 5 mL vial is green and the cap color for the 10 mL vial is royal blue. Each vial is contained in a transparent blister pack consisting of a tray with a lid. The 5 mL vial contains 11 mg powder for solution for injection and the 10 mL vial contains 38.5 mg powder for solution for injection.

Velcade is available in cartons containing 1 single use vial.

Instructions for Use and Handling and Disposal
Administration Precautions
Velcade is an antineoplastic. Caution should be used during handling and preparation.
Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of Velcade was not associated with tissue damage.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.
There have been fatal cases of inadvertent intrathecal administration of Velcade. Velcade is for IV and subcutaneous use only**. DO NOT ADMINISTER VELCADE INTRATHECALLY.**

Reconstitution/Preparation for Intravenous and Subcutaneous Administration
The contents of each vial should be reconstituted only with normal (0.9%) saline according to the following instructions based on route of administration:

	IV		SC
	1 mg bortezomib	3.5 mg bortezomib	3.5 mg bortezomib
Volume of diluents (0.9% Sodium Chloride) added to reconstitute one vial	1.0 mL	3.5 mL	1.4 mL
Final Concentration after reconstitution (mg/mL)	1.0 mg/mL	1.0 mg/mL	2.5 mg/mL

The reconstituted product should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

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

HARUS DENGAN RESEP DOKTER

HOW SUPPLIED
- Velcade 3.5 mg powder for injection
  Box, 1 vial @ 3.5 mg
  Reg. No.: DKI2155203244A1

  Manufactured by BSP Pharmaceuticals S.p.A. (BSP), Via Appia Km 65,561 (loc. Latina Scalo), 04013 Latina, Italy
  Released by Janssen Pharmaceutica N.V., Beerse, Belgium
  Repacked by Zuellig Pharma Specialty Solution Group Pte. Ltd., Singapore
  Registered by PT Integrated Healthcare Indonesia
  For adverse event and product quality complaint please contact (021) 2935 3935 or drugsafety@jacid.jnj.com

- Velcade 1.0 mg powder for injection
  Box, 1 vial @ 1.0 mg
  Reg. No.: DKI1555202444B1

  Manufactured by BSP Pharmaceutical S.p.A. (BSP), Via Appia Km 65,561 (loc. Latina Scalo), 04013 Latina, Italy
  Released by Janssen Pharmaceutica N.V., Beerse, Belgium
  Imported and distributed by PT Soho Industri Pharmasi
  Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920, Indonesia - (021) 460-5550
  For adverse event and product quality complaint please contact (021) 2935 3935 or drugsafety@jacid.jnj.com

Based on CCDS v.27 25-Feb-2021+ add posology hepatic impairment + HAQ

Informasi Produk untuk Pasien
VELCADE 1 mg dan 3.5 mg serbuk untuk larutan untuk injeksi
Bortezomib

Baca leaflet ini secara keseluruhan dengan hati-hati sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membaca lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter Anda atau apoteker.
- Jika Anda mengalami efek samping yang serius atau jika Anda menemukan efek samping yang tidak tercantum dalam leaflet ini, silakan beritahu dokter Anda atau apoteker. Lihat bagian 4.

Apa isi leaflet ini:

1. Apa Velcade dan apa kegunaannya

Velcade mengandung zat aktif bortezomib, yang disebut 'proteasome inhibitor'. Proteasomes memainkan peranan penting dalam mengendalikan fungsi dan pertumbuhan sel. Dengan mengintervensi fungsi tersebut, bortezomib dapat membunuh sel kanker.

Velcade digunakan untuk pengobatan multiple myeloma (kanker sumsum tulang) pada pasien dengan usia lebih dari 18 tahun:
- Sediaan tunggal (monoterapi) atau kombinasi dengan Pegylated lyposomal-doxorubicin, untuk pasien dengan perburukan penyakit (progresif) setelah sebelumnya menerima setidaknya satu pengobatan yang telah dianggap tidak berhasil.
- Kombinasi dengan obat-obatan yang mengandung melphalan dan prednison, untuk pasien yang sebelumnya belum diobati dan tidak cocok dengan kemoterapi dosis tinggi dengan transplantasi sel punca darah.
- Kombinasi dengan obat-obatan lainnya untuk pasien dengan multiple myeloma yang belum diobati sebelumnya dan memenuhi syarat untuk kemoterapi dosis tinggi diikuti dengan transplantasi sel punca darah.

VELCADE digunakan kombinasi dengan obat-obatan rituximab, cyclophosphamide, doxorubicin dan prednisone untuk pengobatan limfoma sel mantel (sejenis kanker yang mempengaruhi kelenjar getah bening) pada pasien yang belum pernah diobati sebelumnya.
Velcade (bortezomib) untuk injeksi juga diindikasikan untuk pengobatan pasien dengan limfoma sel mantel yang telah menerima setidaknya 1 terapi sebelumnya.

Anda akan diberikan Velcade secara intravena (tersedia sebagai Velcade 1 mg dan Velcade 3.5 mg bubuk untuk larutan untuk injeksi) atau subkutan (tersedia sebagai Velcade 3.5 mg bubuk untuk larutan untuk injeksi).

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Velcade

Jangan gunakan Velcade
- Jika Anda alergi terhadap zat aktif atau salah satu bahan lain dari obat ini (yang tercantum dalam bagian 6)
- jika Anda memiliki masalah paru-paru atau jantung yang parah

Peringatan dan tindakan pencegahan
Anda harus memberitahu dokter Anda jika Anda mengalami salah satu dari hal berikut:

- Kelelahan dan pucat yang bisa jadi merupakan gejala anemia atau sel darah merah yang rendah dalam darah Anda; rentan terhadap infeksi, demam atau gejala seperti flu yang bisa jadi merupakan gejala dari sel darah putih yang rendah dalam darah Anda
- Menjadi lebih rentan terhadap memar, atau pendarahan tanpa cedera jelas (misalnya, perdarahan dari usus, lambung, mulut dan gusi atau pendarahan di otak atau perdarahan dari hati) yang dapat menjadi tanda dari rendahnya jumlah trombosit dalam darah Anda
- Diare, konstipasi, mual atau muntah
- Pingsan, pusing atau gejala pusing di masa lalu
- Gejala adanya gagal ginjal yang dapat menyebabkan kelemahan, sesak napas, lesu, dan kebingungan
- Gejala kerusakan atau perubahan fungsi hati, seperti perubahan warna kuning di mata atau kulit (*jaundice*), mual, muntah, kelemahan dan kelelahan
- Mati rasa, kesemutan, atau nyeri di tangan atau kaki (neuropati) di masa lalu
- Masalah dengan jantung atau tekanan darah termasuk nyeri dada, rasa tidak nyaman di daerah dada, peningkatan/penurunan denyut jantung atau pingsan
- Sesak napas atau batuk atau gejala pernapasan lain, seperti dapat tanda-tanda gangguan yang mempengaruhi paru-paru Anda yang dapat mencegah tubuh Anda -mendapatkan cukup oksigen
- Gerakan tiba-tiba atau gerakan yang tidak terkontrol, tekanan darah tinggi, sakit kepala, mengantuk, kebingungan atau disorientasi, kehilangan penglihatan, dan gangguan visual lainnya. Hal tersebut mungkin tanda-tanda infeksi otak serius dan dokter Anda mungkin menyarankan pengujian lebih lanjut dan tindak lanjut
- Gejala sindrom lisis tumor (komplikasi yang disebabkan oleh produk pemecahan sel tumor mati) seperti kram otot, kelemahan otot, kebingungan, kehilangan penglihatan atau gangguan dan sesak napas

Anda akan diwajibkan untuk tes darah rutin sebelum dan selama pengobatan dengan Velcade untuk memeriksa jumlah sel darah Anda secara teratur.

Anda harus membaca informasi produk dari semua produk obat lain yang akan dikombinasikan dengan Velcade untuk mendapatkan informasi yang berkaitan dengan obat-obat ini sebelum memulai pengobatan dengan Velcade.
Ketika thalidomide digunakan, perhatian khusus untuk melakukan tes kehamilan dan persyaratan pencegahan yang dibutuhkan (lihat Kehamilan dan menyusui di bagian ini).

Anak-anak dan remaja
Velcade tidak boleh digunakan pada anak-anak dan remaja karena tidak diketahui bagaimana obat akan mempengaruhi mereka.

Obat-obatan lain dan Velcade
Tolong beritahu dokter Anda atau apoteker jika Anda sedang mengkonsumsi atau baru saja mengkonsumsi obat lain, termasuk obat-obatan diperoleh tanpa resep dokter.
Secara khusus, beritahu dokter Anda jika Anda menggunakan obat-obatan yang mengandung salah satu dari zat aktif berikut:
- Ketoconazole, digunakan untuk mengobati infeksi jamur
- Ritonavir, digunakan untuk mengobati infeksi HIV
- Rifampisin, antibiotik digunakan untuk mengobati infeksi bakteri
- Carbamazepine, phenytoin atau fenobarbital digunakan untuk mengobati epilepsi
- St. John Wort (*Hypericum perforatum*), digunakan untuk depresi atau kondisi lainnya,
- Antidiabetik, obat yang digunakan untuk mengontrol kadar glukosa darah
- Anti-hipertensi, obat yang digunakan untuk menurunkan tekanan darah
- Obat yang mungkin terkait dengan neuropati perifer (mati rasa, kesemutan, atau nyeri di tangan atau kaki) seperti amiodarone, anti-viral, isoniazid, nitrofurantoin atau statin

Kehamilan dan menyusui
Anda tidak boleh menggunakan Velcade jika Anda sedang hamil, kecuali jelas diperlukan.

Baik pria maupun wanita yang menerima Velcade harus menggunakan kontrasepsi efektif selama dan sampai 3 bulan setelah perawatan. Kalau pun telah melakukan tindakan ini kehamilan terjadi, beritahu dokter Anda segera.

Anda tidak boleh menyusui saat menggunakan Velcade. Diskusikan dengan dokter Anda kapan waktu yang aman untuk memulai kembali menyusui setelah menyelesaikan pengobatan.

Thalidomide menyebabkan cacat lahir dan kematian janin. Ketika Velcade diberikan dalam kombinasi dengan thalidomide Anda harus mengikuti program pencegahan kehamilan untuk thalidomide (lihat leaflet untuk thalidomide).

Mengemudi dan menggunakan mesin
Velcade dapat menyebabkan kelelahan, pusing, pingsan, atau penglihatan kabur. Jangan mengemudi atau mengoperasikan alat atau mesin jika Anda mengalami efek samping tersebut; bahkan jika Anda tidak mengalaminya, Anda harus tetap berhati-hati

3. Cara menggunakan Velcade

Dokter Anda akan menghitung dosis dari Velcade yang disesuaikan dengan tinggi dan berat badan Anda (luas permukaan tubuh). Dosis awal Velcade pada umumnya adalah 1,3 mg/m^2 luas permukaan tubuh diberikan dua kali seminggu.
Pada pengobatan menggunakan Velcade 3.5 mg, setidaknya berikan jarak 72 jam antara dosis berturut-turut Velcade.
Pengobatan kembali dengan Velcade 1 mg dapat dipertimbangkan pada pasien multiple myeloma yang sebelumnya merespon terhadap pengobatan dengan Velcade.
Dokter Anda dapat mengubah dosis dan jumlah siklus pengobatan, tergantung pada respons Anda terhadap pengobatan pada terjadinya efek samping tertentu dan kondisi Anda.

Multiple myeloma dan limfoma sel mantel kambuhan
Ketika Velcade diberikan secara tunggal, sekali siklus pengobatan terdiri dari total 4 dosis. Dosis yang diberikan secara intravena pada hari 1, 4, 8 dan 11, diikuti dengan 10-hari 'waktu istirahat' tanpa pengobatan. Oleh karena itu, durasi siklus pengobatan adalah 21 hari (3 minggu). Anda mungkin menerima hingga 8 siklus (24 minggu).

Multiple myeloma kambuhan
Anda juga dapat diberikan VELCADE bersama dengan obat-obatan pegylated liposomal doxorubicin.
Ketika VELCADE diberikan bersama dengan pegylated liposomal doxorubicin, Anda akan menerima VELCADE secara intravena dengan siklus pengobatan 21 hari dan pegylated liposomal doxorubicin 30 mg/m^2 diberikan pada hari ke-4 dari siklus pengobatan 21 hari VELCADE selama 1 jam secara intravena setelah VELCADE injeksi.
Anda mungkin menerima hingga 8 siklus (24 minggu).

Multiple myeloma yang sebelumnya tidak diobati
Jika Anda belum diobati untuk multiple myeloma sebelumnya, dan **tidak cocok** untuk transplantasi sel punca darah, Anda akan menerima Velcade intravena bersama dengan dua obat lain yang mengandung melphalan dan prednison.
Dalam hal ini, durasi siklus pengobatan adalah 42 hari (6 minggu). Anda akan menerima 9 siklus (54 minggu).
- Dalam siklus 1 sampai 4, Velcade diberikan dua kali seminggu pada hari 1, 4, 8, 11, 22, 25, 29 dan 32.
- Dalam siklus 5 sampai 9, Velcade diberikan sekali seminggu pada hari 1, 8, 22 dan 29.

Melphalan (9 mg/m^2) dan prednisone (60 mg/m^2) diberikan secara oral pada hari ke 1, 2, 3 dan 4 pada minggu pertama setiap siklus.
Setidaknya berikan jarak 72 jam di antara dosis berturut-turut Velcade.

Jika Anda belum diobati untuk multiple myeloma sebelumnya, dan Anda **memenuhi syarat** untuk transplantasi sel punca darah, Anda akan menerima VELCADE intravena bersama dengan kombinasi obat-obatan lainnya, misalnya deksametason sebagai pengobatan induksi.
Ketika VELCADE diberikan bersama dengan deksametason, Anda akan menerima VELCADE intravena dalam dua minggu yaitu pada hari ke 1, 4, 8 dan 11 dengan siklus pengobatan 21 hari dan deksametason 40 mg diberikan

secara oral pada hari 1, 2, 3, 4, 8, 9, 10 dan 11 dari 21 hari siklus pengobatatan VELCADE. Interval pengobatan 3-mingguan ini disebut sebagai satu siklus.

Anda akan menerima 4 siklus (12 minggu) dari kombinasi ini.

Limfoma sel mantel yang sebelumnya tidak diobati
Jika Anda belum diobati untuk limfoma sel mantel sebelumnya, Anda akan menerima VELCADE intravena bersama dengan obat-obatan rituximab, cyclophosphamide, doxorubicin dan prednisone.
VELCADE diberikan secara intravena pada hari 1, 4, 8 dan 11, diikuti dengan 'waktu istirahat' tanpa pengobatan. Durasi siklus pengobatan adalah 21 hari (3 minggu). Anda mungkin menerima hingga 8 siklus (24 minggu).
Berikut obat-obatan lainnya yang diberikan pada hari 1 dari setiap siklus pengobatan Velcade 3 minggu melalui infus intravena: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, dan doxorubicin 50 mg/m^2. Prednisone diberikan secara oral sebanyak 100 mg/m^2 pada hari 1, 2, 3, 4, dan 5 setiap siklus pengobatan.

Bagaimana Velcade diberikan
Velcade akan diberikan oleh tenaga profesional kesehatan yang berpengalaman dalam penggunaan obat sitotoksik.
Obat ini hanya digunakan intravena saja.
Bubuk Velcade harus dilarutkan dahulu sebelum diberikan oleh tenaga profesional kesehatan. Larutan yang dihasilkan kemudian disuntikkan ke pembuluh darah dengan cepat, selama 3 sampai 5 detik.

Jika Anda diberi terlalu banyak VELCADE
Karena obat ini diberikan oleh dokter atau perawat Anda, kecil kemungkinan Anda akan diberikan terlalu banyak. Jika terjadi overdosis, dokter Anda akan memantau Anda untuk efek samping.

4. Kemungkinan efek samping

Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya. Beberapa dari efek ini mungkin serius.

Pengobatan dengan Velcade sangat sering menyebabkan penurunan jumlah sel darah merah dan putih dan trombosit dalam darah Anda. Oleh karena itu, Anda harus mengambil tes darah rutin sebelum dan selama pengobatan dengan Velcade, untuk memeriksa jumlah sel darah Anda secara teratur. Anda mungkin mengalami pengurangan jumlah:
- Trombosit, yang dapat membuat Anda lebih rentan terhadap memar, atau pendarahan tanpa cedera jelas (misalnya, perdarahan dari usus, lambung, mulut dan gusi atau pendarahan di otak atau perdarahan dari hati)
- Sel darah merah, yang dapat menyebabkan anemia, dengan gejala seperti kelelahan dan pucat
- Sel darah putih dapat membuat Anda lebih rentan terhadap infeksi atau gejala seperti flu.

Efek samping yang sangat umum (mempengaruhi lebih dari 1 pengguna dalam 10 orang)
- Sensitivitas, mati rasa, kesemutan atau sensasi terbakar pada kulit, atau nyeri di tangan atau kaki, karena kerusakan saraf
- Pengurangan jumlah sel darah merah dan/atau sel darah putih (lihat Peringatan dan tindakan pencegahan)
- Demam
- Merasa sakit (mual) atau muntah, kehilangan nafsu makan, sakit perut, rasa panas di dada (dispepsia)
- Sembelit dengan atau tanpa kembung (bisa parah)
- Diare: jika hal ini terjadi, penting untuk Anda minum lebih banyak cairan dari biasanya. Dokter Anda mungkin memberikan obat lain untuk mengendalikan diare
- Kelelahan (fatigue), merasa lemas
- Berbagai jenis ruam
- Gangguan tidur
- Penyakit ruam saraf (infeksi herpes, secara lokal termasuk di sekitar mata atau menyebar di seluruh tubuh)
- Nyeri otot, nyeri sendi, nyeri tungkai, kaku otot, edema pada tungkai bawah
- Kurangnya atau kehilangan nafsu makan, nafsu makan berkurang
- Infeksi, termasuk infeksi saluran pernapasan (atas atau bawah), nasopharyngitis, infeksi paru-paru

- Sakit kepala atau pusing
- Batuk atau sulit bernapas
- Ruam kulit

Efek samping yang umum (mempengaruhi 1 sampai 10 pengguna dalam 100 orang)
- Gangguan irama jantung
- Peningkatan detak jantung
- Nyeri dada atau sesak napas dengan olahraga yang mungkin adalah gejala gagal jantung
- Cairan yang berlebihan di sekitar paru-paru, gagal jantung
- Gangguan yang mempengaruhi paru-paru Anda, mencegah tubuh Anda dari mendapatkan cukup oksigen. Beberapa di antaranya adalah kesulitan bernapas, sesak napas, sesak napas tanpa olahraga, pernapasan menjadi pendek, sulit atau berhenti, mengi
- Hidung berair
- Penglihatan kabur
- Infeksi dan iritasi pada lapisan terluar mata dan permukaan bagian dalam kelopak mata (conjunctivitis)
- Luka pada mulut atau bibir, mulut kering, sariawan atau sakit tenggorokan
- Mulas, kembung, bersendawa, masuk angin, sakit perut, pendarahan dari usus atau lambung, gerakan yang buruk dari usus
- Nyeri atau kesulitan dalam menelan
- Tinja berdarah
- Sakit dada
- Kram otot, kejang otot, lemah otot, nyeri pada anggota badan atau punggung
- Dehidrasi
- Abnormal (kelebihan atau kekurangan) kadar glukosa darah dan mengurangi tingkat natrium darah
- Kecemasan
- Perubahan fungsi saraf
- Gerakan yang tidak terkontrol atau tubuh gemetar
- Penurunan fungsi rasa lidah (gangguan indra perasa)
- Pingsan atau sakit kepala ringan, kejang
- Penurunan fungsi ginjal
- Nyeri saat mengeluarkan urin atau ada darah dalam urin
- Perdarahan hidung
- Gatal-gatal
- Peradangan atau perdarahan dari pembuluh darah yang muncul bintik-bintik merah atau ungu kecil (biasanya di kaki) hingga memar besar seperti bercak di bawah kulit atau jaringan
- Infeksi termasuk infeksi saluran kemih, infeksi saluran pernafasan, sinusitis, faringitis, infeksi paru-paru, batuk berdahak, flu seperti penyakit, infeksi usus, infeksi jamur di mulut, dan kondisi berat seperti bakteri dalam aliran darah dan sepsis
- Tekanan darah rendah atau tekanan darah rendah yang terjadi ketika Anda berdiri dari duduk atau berbaring.
- Peningkatan kadar enzim hati
- Cairan yang mengandung vesikel (infeksi Herpes simpleks) atau nyeri setelah pemulihan infeksi herpes (*postherpetic neuralgia*)
- Komplikasi terkait kateter -
- Keletihan
- Nyeri saraf

Efek samping yang tidak umum/jarang (mempengaruhi kurang dari 1 pengguna dalam 100 orang)
- Nyeri dada, ketidaknyamanan dada, peningkatan atau penurunan denyut jantung dan syok yang berhubungan dengan penyakit jantung
- Gangguan pendengaran
- Sendawa, aliran naik-turun atau muntah
- Ulkus lidah
- Muntah darah
- Bintik merah atau ungu kecil di bawah kulit bagian dalam mulut

- Kegagalan gerakan maju isi usus yang normal
- Tingkat abnormal rendah dari semua jenis sel darah yang diproduksi oleh sumsum tulang
- Komplikasi serius (infeksi, demam) karena penurunan jumlah satu jenis sel darah putih
- Gangguan terkait tempat suntikan atau alat suntik (nyeri, iritasi, peradangan atau infeksi)
- Gangguan fungsi hati, peradangan hati, hepatitis
- Batuk berdarah
- Kehilangan fungsi rasa di lidah
- Penurunan kesadaran
- Pendarahan di otak
- Hipersensitifitas obat termasuk reaksi hipersensitifitas parah dan berpotensi fatal yang melibatkan kulit dan membran mukosa
- Kondisi otak yang parah yang bisa pulih kembali, meliputi kejang, tekanan darah tinggi, sakit kepala, kelelahan, kebingungan, kebutaan atau masalah penglihatan lainnya.
- Penyakit paru-paru yang parah
- Sindrom Tumor lisis (lihat Peringatan & tindakan pencegahan)

Efek samping yang jarang (mempengaruhi 1 dari 1.000 orang)

- Peradangan saraf yang serius, yang dapat menyebabkan kelumpuhan dan kesulitan bernapas (*sindrom Guillain-Barré*)

Pelaporan efek samping

Jika salah satu dari efek samping menjadi serius atau jika Anda menemukan efek samping yang tidak tercantum dalam leaflet ini, silakan beritahu dokter Anda atau apoteker segera.

Anda juga dapat melaporkan efek samping secara langsung melalui sistem pelaporan Badan Pengawas Obat dan Makanan Nasional melalui salah satu metode berikut:

- Telepon: (021) 4244691 ext.1072
- Fax: (021) 42883485
- Online: http://e-meso.pom.go.id

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5. Bagaimana menyimpan Velcade

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Jangan menggunakan obat ini setelah tanggal kadaluwarsa yang tertera pada botol dan karton setelah EXP.
Jangan simpan di atas suhu 30^0C. Jaga botol tetap di dalam dus agar terlindung dari cahaya.

Larutan rekonstitusi harus digunakan segera setelah disiapkan. Jika larutan rekonstitusi tidak digunakan segera, penggunaan selama waktu penyimpanan dan kondisi sebelum penggunaan adalah tanggung jawab pengguna. Namun, larutan rekonstitusi akan stabil selama 8 jam pada suhu 25°C disimpan dalam kemasan asli dan/atau jarum suntik, dengan total waktu penyimpanan untuk obat rekonstitusi tidak melebihi 8 jam sebelum pemberian.

Kemasan Velcade hanya untuk sekali pakai. Setiap produk atau limbah bahan yang tidak terpakai harus dibuang sesuai dengan persyaratan lokal.

6. Isi kemasan dan informasi lainnya

Apa isi velcade

- Zat aktif adalah bortezomib. Setiap vial mengandung 1 mg dan 3.5 mg bortezomib (sebagai ester mannitol boron).

  Rekonstitusi intravena:
  Setelah rekonstitusi, 1 ml larutan untuk injeksi intravena mengandung 1 mg bortezomib.

Rekonstitusi subkutan:
Setelah rekonstitusi, 1 ml larutan untuk injeksi subkutan mengandung 2.5 mg bortezomib.

- Zat tambahan lain adalah mannitol (E421) dan nitrogen

Seperti apa Velcade dan isi kemasan
Serbuk VELCADE untuk larutan untuk injeksi adalah serbuk berwarna putih hingga *off-white*.
Setiap dus Velcade 1 mg serbuk untuk larutan untuk injeksi berisi botol kaca dengan tutup hijau, dan Velcade 3.5 mg serbuk untuk larutan untuk injeksi berisi botol kaca dengan tutup biru, dalam kemasan blister transparan.

HARUS DENGAN RESEP DOKTER

- **Velcade 3.5mg**
  No. Reg. : DKI2155203244A1
  Dibuat oleh: BSP Pharmaceuticals S.p.A. (BSP), Via Appia Km 65,561 (loc. Latina Scalo), 04013 Latina, Italy
  Didaftarkan oleh: PT Integrated Healthcare Indonesia, Jakarta – Indonesia

- **Velcade 1mg**
  No. Reg. : DKI1555202444B1
  Dibuat oleh: BSP Pharmaceuticals S.p.A. (BSP), Via Appia Km 65,561 (loc. Latina Scalo), 04013 Latina, Italy
  Pemilik Izin Edar: PT Soho Industri Pharmasi
  Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920, Indonesia – telp (021) 460-5550

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935

Based on CCDS v.27 25-Feb-2021 + HAQ (add posology hepatic impairment)