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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Millennium Pharmaceuticals, Inc., I respectfully request the NCCN Multiple Myeloma Guidelines Panel to review the enclosed data on the subcutaneous administration of VELCADE® (bortezomib) in patients with multiple myeloma.

Specific Changes:
Inclusion of an additional specific footnote on bortezomib in the Myeloma Therapy section (MYEL-D) of the NCCN Clinical Practice Guidelines (NCCN Guidelines™) in Multiple Myeloma, indicating:

- "Bortezomib may be administered either by subcutaneous injection or as a bolus intravenous injection"
- "Starting bortezomib subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy."

These statements reflect the recently approved updates to the United States Prescribing Information (included below).

In addition, we believe that similar statements are warranted within the narrative section of the Guidelines (for example, MS-6, where bortezomib adverse events are described; and elsewhere as appropriate).

FDA Clearance: The FDA has approved VELCADE for the treatment of multiple myeloma; the recommended dose of VELCADE is 1.3 mg/m^2 administered either as a 3- to 5-second bolus intravenous injection or subcutaneous injection. The recently approved updated US Prescribing Information notes that "Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy." Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

Rationale: The primary report of the phase III MMY-3021 study of subcutaneous versus intravenous administration of bortezomib was published in 2011 in The Lancet Oncology. The findings of this study demonstrated non-inferior efficacy with subcutaneous versus intravenous bortezomib with regards to the primary endpoint (overall response rate after 4 cycles of single-agent bortezomib). Consistent results were shown with regards to secondary endpoints. The results of this study are reflected in the recently approved updates to the US Prescribing Information, as described.

The following enclosures are submitted in support of the above proposed changes.

- Moreau P et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol.* 2011;12:431-440.
- VELCADE (bortezomib) for Injection. United States prescribing information, Rev 13, issued January 2012.

Yours sincerely

Oliver Rosen, MD
Vice President, Global Medical Affairs

Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study

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Summary

Background Intravenous injection is the standard administration route of bortezomib; however, subcutaneous administration is an important alternative. We compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1·3 mg/m² dose and twice per week schedule in patients with relapsed multiple myeloma.

Methods This randomised, phase 3 study was undertaken at 53 centres in ten countries in Europe, Asia, and South America. Patients aged 18 years and older with relapsed multiple myeloma after one to three previous lines of therapy were randomly assigned to receive up to eight 21-day cycles of bortezomib 1·3 mg/m², on days 1, 4, 8, and 11, by subcutaneous injection or intravenous infusion. Randomisation was by an interactive voice response system based on a computer-generated randomisation schedule, stratified by number of previous lines and disease stage. Patients and treating physicians were not masked to treatment allocation. The primary objective was to show non-inferiority of subcutaneous versus intravenous bortezomib in terms of overall response rate (ORR) after four cycles in all patients with a diagnosis of measurable, secretory multiple myeloma who received one or more dose of drug (response-evaluable population). Non-inferiority was defined as retaining 60% of the intravenous treatment effect. This study is registered with ClinicalTrials.gov, number NCT00722566, and is ongoing for long-term follow-up.

Findings 222 patients were randomly assigned to receive subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups. ORR after four cycles was 42% in both groups (61 patients in subcutaneous group and 31 in intravenous group; ORR difference –0·4%, 95% CI –14·3 to 13·5), showing non-inferiority (p=0·002). After a median follow-up of 11·8 months (IQR 7·9–16·8) in the subcutaneous group and 12·0 months (8·1–15·6) in the intravenous group, there were no significant differences in time to progression (median 10·4 months, 95% CI 8·5–11·7, *vs* 9·4 months, 7·6–10·6; p=0·387) and 1-year overall survival (72·6%, 95% CI 63·1–80·0, *vs* 76·7%, 64·1–85·4; p=0·504) with subcutaneous versus intravenous bortezomib. Grade 3 or worse adverse events were reported in 84 (57%) patients in the subcutaneous group versus 52 (70%) in the intravenous group; the most common were thrombocytopenia (19 [13%] *vs* 14 [19%]), neutropenia (26 [18%] *vs* 13 [18%]), and anaemia (18 [12%] *vs* six [8%]). Peripheral neuropathy of any grade (56 [38%] *vs* 39 [53%]; p=0·044), grade 2 or worse (35 [24%] *vs* 30 [41%]; p=0·012), and grade 3 or worse (nine [6%] *vs* 12 [16%]; p=0·026) was significantly less common with subcutaneous than with intravenous administration. Subcutaneous administration was locally well tolerated.

Interpretation Subcutaneous bortezomib offers non-inferior efficacy to standard intravenous administration, with an improved safety profile.

Funding Johnson & Johnson Pharmaceutical Research and Development, and Millennium Pharmaceuticals.

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See Comment page 410

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Introduction

The introduction of the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide have contributed to improvements in overall survival in patients with multiple myeloma.[1] Bortezomib-based therapies are suggested as standards of care in patients with newly diagnosed and relapsed multiple myeloma,[2,3] including the approved indication of bortezomib plus melphalan and prednisone for previously untreated patients who are ineligible for stem-cell transplantation,[4,5] bortezomib-based induction regimens for transplant patients,[6,7] and the approved indication of bortezomib alone or in combination with pegylated liposomal doxorubicin for patients with relapsed multiple myeloma.[8–10]

The recommended dose and schedule of bortezomib is 1·3 mg/m² administered as a 3–5-s bolus intravenous injection on days 1, 4, 8, and 11 of 21-day cycles.[11,12] This regimen is active and well tolerated in patients with relapsed multiple myeloma.[8,9,13–15] As an alternative to

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intravenous delivery, subcutaneous administration of bortezomib could be a good option for patients, particularly those with poor venous access. Subcutaneous administration eliminates the need for repeated intravenous access or insertion of long-term central venous access devices, improving convenience for patients and physicians. Subcutaneous administration is used for several antineoplastic agents that are not directly toxic to tissues, such as alemtuzumab.[16]

In a randomised phase 1 trial of subcutaneous versus intravenous bortezomib in 24 patients with relapsed or refractory multiple myeloma, both administration routes, with the standard injection concentration of 1 mg/mL, showed similar systemic bortezomib exposure and 20S proteasome inhibition levels.[17] Response rates and safety profile seemed to be similar for both administration routes, with good local tolerability of subcutaneous injections.[17]

In this international, multicentre, randomised phase 3 study we investigated the efficacy and safety of subcutaneous and intravenous bortezomib at the approved 1·3 mg/m² dose and twice per week schedule in patients with relapsed multiple myeloma.[11,12] In a subset of patients, we characterised the pharmacokinetics and pharmacodynamics of subcutaneous and intravenous bortezomib.

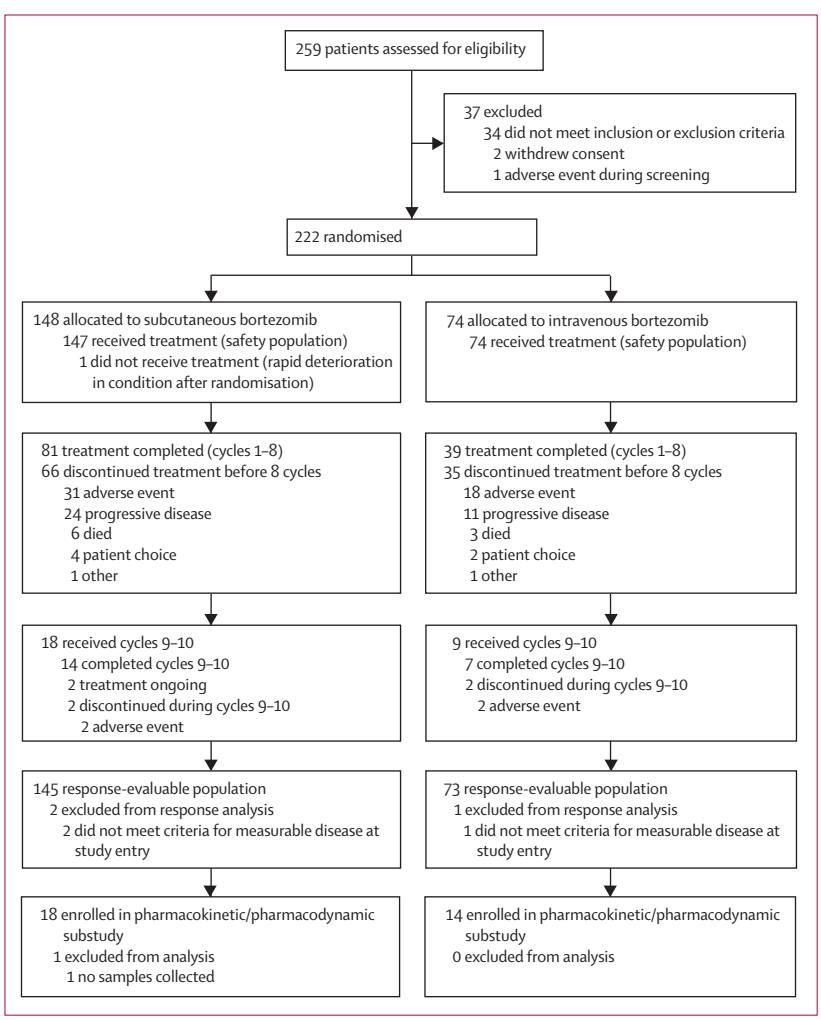

Figure 1: **Trial profile**

Methods

Study design and patients

This randomised, open-label, phase 3 study was undertaken at 53 centres in ten countries in Europe, Asia, and South America. Patients were enrolled between July 16, 2008, and Feb 26, 2010. Clinical data cutoff was Aug 31, 2010, 30 days after the last patient had completed eight treatment cycles.

Eligible patients were aged 18 years and older; had measurable, secretory multiple myeloma; had received one to three previous lines of therapy; and had evidence of disease progression since last therapy. Patients had to have Karnofsky performance status (KPS) of 70% or more and adequate haematological, hepatic, and renal function. Exclusion criteria were previous bortezomib treatment; grade 2 or higher peripheral neuropathy or neuropathic pain; or antineoplastic or experimental therapy or corticosteroids (>10 mg per day prednisone or equivalent) within 3 weeks before randomisation.

All patients provided written informed consent. The study was approved by the relevant review board or independent ethics committee at each participating institution, and was undertaken according to the provisions of the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to receive up to eight 21-day cycles of bortezomib 1·3 mg/m² on days 1, 4, 8, and 11, administered by subcutaneous or intravenous injection. Patients were assigned by means of an interactive voice response system based on a computer-generated randomisation schedule prepared by the sponsor. Central randomisation with permuted blocks was used. Stratification factors were number of lines of previous therapy (one *vs* more than one) and international staging system (ISS)[18] stage. Patients and treating physicians were not masked to treatment allocation.

Procedures

The primary objective was to show that subcutaneous bortezomib is not inferior to intravenous bortezomib in terms of overall response rate (ORR; complete response [CR] plus partial response [PR]) after four cycles of single-agent treatment. Secondary objectives were to establish CR, near CR, and very good PR rates after four cycles; ORR after eight cycles, including the effect of addition of dexamethasone; time to response; duration of response; time to progression; progression-free survival; and 1-year overall survival. Other secondary

objectives were to assess safety and tolerability, including local tolerability of subcutaneous administration, and pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous bortezomib.

Patients with suboptimum response (<CR, without disease progression) at the end of cycle 4 could additionally receive oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 from cycle 5 onwards. Patients with stable disease or PR as best response at the end of cycle 8 who were evolving steadily to late PR or CR, respectively, could receive two additional cycles.

Dose reductions for bortezomib and dexamethasone were needed for prespecified non-haematological toxic effects. Bortezomib-related peripheral neuropathy or neuropathic pain was managed according to the standard prespecified dose-modification algorithm. All concomitant drugs for supportive care were allowed, as indicated, apart from systemic steroids and antineoplastic therapies with antimyeloma effects. Bisphosphonates were administered according to established guidelines.[19]

Subcutaneous injections were administered at 2·5 mg/mL (3·5 mg bortezomib reconstituted with 1·4 mL normal [0·9%] saline) to limit the volume injected. Subcutaneous injection sites were the thighs or abdomen; sites were rotated for successive injections. Injections at the same site within a cycle were avoided. Alternation between right and left abdomen, upper and lower quadrant, or right and left thigh, proximal and distal sites, was recommended in the protocol. Intravenous injections were administered at a concentration of 1 mg/mL (3·5 mg bortezomib reconstituted with 3·5 mL normal [0·9%] saline) as a 3–5-s intravenous push.[11,12]

Disease response was assessed by a validated computer algorithm[5,8] with use of previously blinded review for data consistency and completeness with criteria from the European Group for Blood and Marrow Transplantation (EBMT),[20] incorporating near CR[14] and very good PR.[21] In each group, we collected blood and 24-h urine samples for M-protein measurement at baseline, every 3 weeks (day 1 of each cycle) during the 24-week treatment period, at the end-of-treatment visit, and then every 8 weeks until disease progression. M-protein assessments were done by a central laboratory that was masked to group assignment. Bone marrow aspiration and biopsy were done for all patients at screening and as needed for confirmation of CR or diagnosis of progression.

After treatment and documentation of progression, patients were followed up every 12 weeks for survival and subsequent therapies. Adverse events were monitored until 30 days after the last dose of study drug and graded according to National Cancer Institute common terminology criteria for adverse events (version 3.0).[22] Tolerability of subcutaneous administration at the local injection site was systematically assessed by investigators at 2–4 h after

	Subcutaneous bortezomib (N=148)	Intravenous bortezomib (N=74)
Age (years)	64·5 (42–88)	64·5 (38–86)
Age ≥65 years	74 (50%)	37 (50%)
Men	74 (50%)	47 (64%)
Ethnic origin		
White	143 (97%)	71 (96%)
Asian	5 (3%)	3 (4%)
Weight (kg)	73 (43–132)	75 (42–109)
Region		
Western Europe	43 (29%)	30 (41%)
Eastern Europe	97 (66%)	33 (45%)
Non-European	8 (5%)	11 (15%)
Karnofsky performance status		
70%	32 (22%)	12 (16%)
80%	57 (39%)	24 (32%)
≥90%	59 (40%)	38 (51%)
Previous lines of therapy*		
1	92 (62%)	48 (65%)
>1	56 (38%)	26 (35%)
Time since last line of therapy (months)	3·4 (0·3–144)	5·8 (0·6–105)
Last line >6 months before study	63 (43%)	36 (49%)
Any previous IMiD	62 (42%)	39 (53%)
IMiD as last therapy	58 (39%)	35 (47%)
Myeloma type		
IgG	96 (65%)	53 (72%)
IgA	38 (26%)	14 (19%)
IgD	1 (1%)	0
IgM	1 (1%)	1 (1%)
Light chain	12 (8%)	6 (8%)
ISS stage*		
I	40 (27%)	20 (27%)
II	60 (41%)	30 (41%)
III	48 (32%)	24 (32%)
Lytic bone lesions†		
0	25 (17%)	16 (22%)
1–3	24 (16%)	12 (16%)
4–10	30 (20%)	11 (15%)
>10	69 (47%)	34 (46%)
Cytogenetics‡		
Standard risk	118 (86%)	56 (81%)
High risk§	19 (14%)	13 (19%)
β_2 microglobulin (mg/L)	4·20 (1·7–38·4)	4·25 (1·6–19·4)
Albumin (g/L)	35·5 (20–46)	36·0 (21–46)
Creatinine clearance (mL/min)	67.5 (23–144)	73 (28–150)
Creatinine clearance ≤60 mL/min	60 (41%)	24 (32%)
Haemoglobin (g/L)	107 (73–156)	111 (81–165)
Neutrophils (×10⁹/L)	2·8 (0·8–11·7)	2·6 (1·0–9·4)
Platelets (×10⁹/L)	207·0 (50–571)	207·5 (55–433)

Data are median (range) or number (%). IMiD=immunomodulatory drug. ISS=international staging system. *Stratification factor. †Data missing for one patient in intravenous group. ‡n=137 in subcutaneous group and n=69 in intravenous group. §High-risk cytogenetics (n/number tested) consisted of: deletion 17p by FISH or karyotype (11/122 [9%] in subcutaneous group *vs* five of 58 [9%] in intravenous group), t(4;14) by FISH or karyotype (eight of 124 [6%] *vs* five of 62 [8%]), t(14;16) by FISH (one of 65 [2%] *vs* four of 25 [16%]), deletion 13 by karyotype (three of 44 [7%] *vs* two of 29 [7%]), or hypoploidy by karyotype (none of 44 *vs* none of 29).

Table 1: **Patient demographics and baseline characteristics**

	Subcutaneous bortezomib (N=147)*	Intravenous bortezomib (N=74)
Number of treatment cycles	8 (1–10)	8 (1–10)
Time on study treatment (weeks)	22·6 (0·1–33·1)	22·6 (0·6–30·7)
Bortezomib cumulative dose (mg/m²)	33·76 (1·2–52·8)	31·46 (2·6–51·8)
Bortezomib dose intensity (mg/m² per cycle, cycles 1–4)	5·13 (1·2–5·3)	4·89 (2·4–5·4)
Bortezomib dose intensity (mg/m² per cycle, cycle ≥5)	4·88 (1·3–5·3)	4·91 (1·4–5·5)
Patients receiving dexamethasone	82 (56%)	39 (53%)
Dexamethasone dose intensity (mg per cycle)	160 (40–163·3)	160 (72–160)

Data are median (range) or number (%). *Three patients in the subcutaneous group had protocol violations for route of administration; in one patient, the subcutaneous injection site was not rotated, and two patients also received intravenous injections by error on at least one occasion.

Table 2: **Treatment exposure**

	Subcutaneous bortezomib (N=145)*	Intravenous bortezomib (N=73)*
Response after 4 cycles (single-agent bortezomib), primary endpoint		
ORR (CR+PR)†	61 (42%)	31 (42%)
CR‡	9 (6%)	6 (8%)
PR	52 (36%)	25 (34%)
nCR	9 (6%)	4 (5%)
VGPR	6 (4%)	2 (3%)
CR+nCR	18 (12%)	10 (14%)
≥VGPR	24 (17%)	12 (16%)
Minimal response	20 (14%)	10 (14%)
ORR+minimal response§	81 (56%)	41 (56%)
No change	49 (34%)	25 (34%)
Progressive disease	9 (6%)	5 (7%)
Not evaluable	6 (4%)	2 (3%)
Response after 8 cycles (bortezomib with or without dexamethasone)		
ORR (CR + PR)¶	76 (52%)	38 (52%)
CR‡	15 (10%)	9 (12%)
PR	61 (42%)	29 (40%)
nCR	14 (10%)	7 (10%)
VGPR	7 (5%)	2 (3%)
CR+nCR	29 (20%)	16 (22%)
≥VGPR	36 (25%)	18 (25%)
Minimal response	14 (10%)	11 (15%)
ORR+minimal response§	90 (62%)	49 (67%)
No change	40 (28%)	17 (23%)
Response improvement (from cycle 4 to 8) in patients who received dexamethasone‖		
PR to CR‡	4/31 (13%)	2/15 (13%)
<PR to PR	14/47 (30%)	7/23 (30%)

Data are number (%). ORR=overall response rate. CR=complete response. PR=partial response. nCR=near complete response. VGPR=very good partial response. *Four patients were not evaluable for response, three in the subcutaneous group and one in the intravenous group. One patient in the subcutaneous group did not receive any treatment; the other two patients in the subcutaneous group and the patient in the intravenous group did not meet the criteria for measurable disease at study entry. †For the non-inferiority hypothesis, p=0·002. ‡CR confirmed by bone marrow assessment. Two additional patients improved from PR to CR in the subcutaneous group after cycles 9–10 of treatment. §For the non-inferiority hypothesis, p<0·0001. ¶For the non-inferiority hypothesis, p=0·0001. ‖n=82 in subcutaneous group and n=39 in intravenous group.

Table 3: **Rates of response to treatment by group in the response-evaluable population**

each injection in cycle 1 and at their discretion thereafter. Between visits, patients documented the outcome of injection-site reactions with a detailed diary.

Pharmacokinetic and pharmacodynamic assessments

We undertook a pharmacokinetic and pharmacodynamic substudy at selected sites. Blood samples were collected in cycle 1 on day 1 before the dose was given, on day 11 before the dose, and at several timepoints after dosing. Bortezomib plasma concentrations were measured with a validated liquid chromatography coupled to tandem mass spectrometry method. Pharmacokinetic parameters were estimated by non-compartmental analysis of plasma concentration–time data. We analysed whole blood samples to measure 20S proteasome chymotryptic activity, with a standard method.[23] Pharmacodynamic parameters were calculated by analysis of percentage inhibition of 20S proteasome activity–time data.

Statistical analysis

The study was designed to establish whether subcutaneous bortezomib was non-inferior to intravenous administration, which was defined as retaining 60% of the intravenous treatment effect, measured by ORR, at the end of four cycles. To declare non-inferiority, the lower bound of the 95% CI for ORR with subcutaneous administration minus $0{\cdot}6 \times$ORR with intravenous administration needed to be 0 or greater. A sample size of about 216 patients (144 in subcutaneous group, 72 in intravenous group) was needed to show non-inferiority of subcutaneous versus intravenous bortezomib, assuming the ORR in both groups to be 35·5% (lower limit of 95% CI for pooled ORR after four cycles from previous phase 3 studies of single-agent bortezomib[8,10]) and a one-sided α level of 0·025 and about 80% power.

As specified in the protocol, the primary efficacy endpoint and other secondary response endpoints were analysed in the response-evaluable population (all patients with a diagnosis of measurable, secretory multiple myeloma who received one or more dose of drug) by treatment randomisation. Time to progression, progression-free survival, and 1-year overall survival were analysed in the intention-to-treat population. We estimated time-to-event distributions for each group with the Kaplan-Meier method. Adverse events were analysed in the safety population (patients who received one or more dose of drug). Statistical analyses were done with SAS (version 9.1.3).

Pharmacokinetics and pharmacodynamics were analysed in patients who completed all assessments during cycle 1 without dose omission or reduction; about 18 patients per administration route were needed to ensure at least 12 assessable patients in each group.

This study is registered with ClinicalTrials.gov, number NCT00722566, and with EudraCT, number 2008-000952-28.

Role of the funding source
Representatives of the study sponsors were involved in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

222 patients were randomly assigned to receive subcutaneous (n=148) or intravenous (n=74) bortezomib (figure 1); one patient in the subcutaneous group discontinued before treatment started. Patient demographics and baseline characteristics were similar between groups (table 1), with some exceptions. By chance, in the subcutaneous group, a higher proportion of patients had KPS 80% or less, had creatinine clearance of 60 mL per min or less, and were from eastern Europe; in the intravenous group, more patients were men and had high-risk cytogenetics (table 1).

In both groups, patients received a median of eight cycles (range one to ten; table 2). The median cumulative dose of bortezomib was much the same in each group (table 2), as was the proportion of patients who received bortezomib in combination with dexamethasone after cycle 4 (table 2). 12% of patients in each group (18 in subcutaneous group and nine in intravenous group) continued onto cycles 9 and 10.

ORR after four cycles of single-agent bortezomib was 42% in both the subcutaneous (61 of 145 patients) and intravenous (31 of 73 patients) groups (table 3), including 18 (12%) and ten (14%) patients with CR or near CR, respectively. The p value for the non-inferiority hypothesis was 0·002, proving the primary hypothesis of non-inferiority in ORR after four cycles. The ORR difference was –0·4% (95% CI –14·3 to 13·5), with a relative risk of 0·99 (0·71–1·37). We undertook a sensitivity analysis with a per-protocol population (patients in the response-evaluable population excluding those with major protocol deviations that might affect response evaluation; 132 patients in the subcutaneous group and 68 in the intravenous group), which confirmed the findings of the primary efficacy endpoint (data not shown).

Response rates were similar between groups after four cycles (single-agent bortezomib) and eight cycles (bortezomib with and without dexamethasone); ORR after eight cycles was 52% in both groups (76 of 145 patients in the subcutaneous group, 38 of 73 in the intravenous group), with 29 (20%) subcutaneous and 16 (22%) intravenous patients achieving CR or near CR, and 36 (25%) and 18 (25%) achieving at least very good PR, respectively (table 3). We recorded response improvements from cycle 4 to cycle 8 in both groups in patients who received dexamethasone (table 3). Best M-protein responses were similar between groups (webappendix p 1).

See Online for webappendix

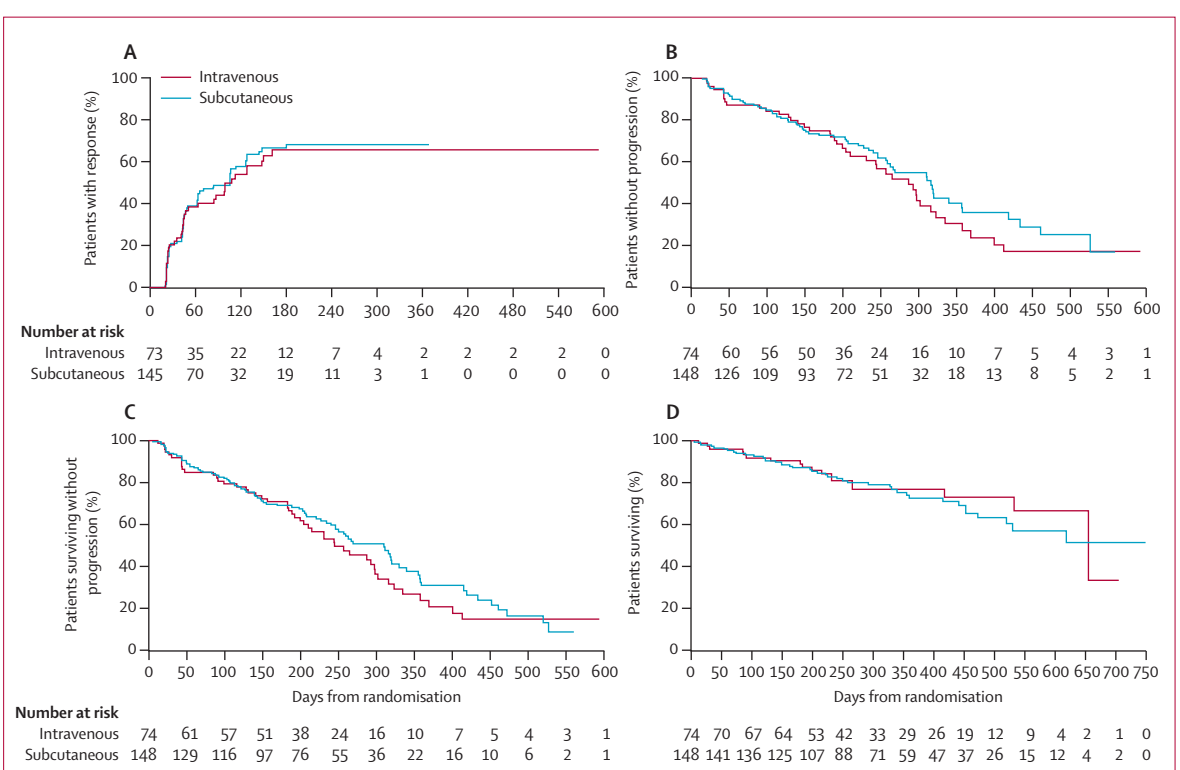

Figure 2: **Kaplan-Meier estimates of time to response in the response-evaluable population (A), and time to disease progression (B), progression-free survival (C), and overall survival (D) in the intention-to-treat population**

	Subcutaneous bortezomib (N=147)		Intravenous bortezomib (N=74)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	140 (95%)	84 (57%)	73 (99%)	52 (70%)
Any treatment-related AE	124 (84%)	58 (39%)	67 (91%)	41 (55%)
MedDRA system organ class				
Blood and lymphatic system disorders	86 (59%)	49 (33%)	40 (54%)	25 (34%)
Eye disorders	15 (10%)	0	10 (14%)	0
Gastrointestinal disorders	55 (37%)	10 (7%)	43 (58%)	5 (7%)
General disorders and administration site conditions	79 (54%)	11 (7%)	43 (58%)	9 (12%)
Hepatobiliary disorders	16 (11%)	5 (3%)	7 (9%)	1 (1%)
Infections* and infestations	72 (49%)	15 (10%)	40 (54%)	11 (15%)
Metabolism and nutrition disorders	41 (28%)	9 (6%)	21 (28%)	4 (5%)
Musculoskeletal and connective tissue disorders	48 (33%)	2 (1%)	29 (39%)	6 (8%)
Nervous system disorders	82 (56%)	20 (14%)	49 (66%)	17 (23%)
Psychiatric disorders	22 (15%)	1 (1%)	12 (16%)	1 (1%)
Renal and urinary disorders	21 (14%)	8 (5%)	6 (8%)	3 (4%)
Respiratory, thoracic, and mediastinal disorders	34 (23%)	7 (5%)	26 (35%)	7 (9%)
Skin and subcutaneous tissue disorders	35 (24%)	4 (3%)	13 (18%)	0
Vascular disorders	28 (19%)	3 (2%)	13 (18%)	2 (3%)
Treatment discontinuations because of AEs	33 (22%)	..	20 (27%)	..
Bortezomib dose reductions because of AEs	46 (31%)	..	32 (43%)	..
Serious AEs	53 (36%)	..	26 (35%)	..
Deaths within 30 days of last dose of treatment†	8 (5%)	..	5 (7%)	..

Data are number of patients (%). Some patients might have had several AEs. AE=adverse event. MedDRA=Medical Dictionary for Regulatory Activities. *Prophylactic antiviral therapy for prevention of herpes zoster reactivation was at the investigator's discretion; overall rates of herpes zoster were 16 (11%), including two (1%) grade 3 events, in the subcutaneous group; and seven (9%), including one (1%) grade 3 event, in the intravenous group. †Deaths in the subcutaneous group included four attributable to AEs (two considered related to treatment of pneumonia and sudden death); deaths in the intravenous group were all attributable to AEs (one considered related to treatment of coronary artery insufficiency).

Table 4: **Summary of safety profile by treatment group, including rates of adverse events according to system organ class**

	Subcutaneous bortezomib (N=147)		Intravenous bortezomib (N=74)	
	All grades	Grade ≥3	All grades	Grade ≥3
Anaemia	53 (36%)	18 (12%)	26 (35%)	6 (8%)
Thrombocytopenia	52 (35%)	19 (13%)	27 (36%)	14 (19%)
Peripheral sensory neuropathy	51 (35%)	7 (5%)	36 (49%)	11 (15%)
Neutropenia	42 (29%)	26 (18%)	20 (27%)	13 (18%)
Diarrhoea	35 (24%)	3 (2%)	27 (36%)	4 (5%)
Neuralgia	35 (24%)	5 (3%)	17 (23%)	7 (9%)
Leukopenia	29 (20%)	9 (6%)	16 (22%)	5 (7%)
Pyrexia	28 (19%)	0	12 (16%)	0
Nausea	27 (18%)	0	14 (19%)	0
Asthenia	23 (16%)	3 (2%)	14 (19%)	4 (5%)
Weight decreased*	22 (15%)	0	2 (3%)	1 (1%)
Constipation	21 (14%)	1 (1%)	11 (15%)	1 (1%)
Fatigue	17 (12%)	3 (2%)	15 (20%)	3 (4%)
Vomiting	17 (12%)	3 (2%)	12 (16%)	1 (1%)
Pneumonia	12 (8%)	8 (5%)	7 (9%)	6 (8%)
Haematology laboratory data†				
Haemoglobin	144 (98%)	21 (14%)	72 (97%)	9 (12%)
White blood cell count	117 (80%)	12 (8%)	65 (88%)	13 (18%)
Absolute neutrophil count	99 (67%)	32 (22%)	57 (77%)	21 (28%)
Platelets	130 (88%)	26 (18%)	69 (93%)	17 (23%)

Data are number of patients (%). Some patients might have had several adverse events. *As reported as adverse events. By objective bodyweight data analysis, 105 (71%) patients in the subcutaneous group and 51 (69%) in the intravenous group lost weight during the study, including 32 (22%) and 12 (16%) with objective grade 1 weight loss, 19 (13%) and nine (12%) with grade 2, and none and one (1%) with grade 3, respectively. †Haematology laboratory data were graded according to National Cancer Institute common terminology criteria for adverse events (version 3.0).

Table 5: **Rates of adverse events of any grade in 15% or more of patients and of grade 3 or higher in 5% or more of patients in either treatment group, and haematology parameters**

Median time to first response (response-evaluable analysis) was 3·5 months in both groups (95% CI 2·1–4·2 in the subcutaneous group and 1·7–5·3 in the intravenous group; HR 1·059, 95% CI 0·716–1·567; p=0·772; figure 2). In responding patients, median time to first response was 1·4 months (range 0·7–5·9) in the subcutaneous group and 1·4 months (0·7–5·3) in the intravenous group, and median time to best response was 1·6 months (0·7–9·1) and 1·5 months (0·7–6·3), respectively. Median duration of response was 9·7 months (95% CI 8·4–15·3) and 8·7 months (7·6–12·1), respectively.

After a median follow-up of 11·8 months (IQR 7·9–16·8) in the subcutaneous group and 12·0 months (8·1–15·6) in the intravenous group, we noted no significant difference in time to progression (median 10·4 months, 95% CI 8·5–11·7, in the subcutaneous group *vs* 9·4 months, 7·6–10·6, in the intravenous group; HR 0·839, 95% CI 0·564–1·249; p=0·387); progression-free survival (median 10·2 months, 95% CI 8·1–10·9, *vs* 8·0 months, 6·7–9·8; HR 0·824, 95% CI 0·574–1·183; p=0·295); and overall survival (1-year survival 72·6%, 95% CI 63·1–80·0, *vs* 76·7%, 64·1–85·4; p=0·504) between groups (intention-to-treat analysis; figure 2).

Tables 4 and 5 show the safety profiles of subcutaneous and intravenous bortezomib. Grade 3 and higher adverse events were reported in 84 of 147 (57%) patients in the subcutaneous group and 52 of 74 (70%) in the intravenous group, with 33 (22%) and 20 (27%) discontinuing treatment because of adverse events, and 46 (31%) and 32 (43%) needing bortezomib dose reductions because of adverse events, respectively. Serious adverse events were reported in a similar proportion of patients (table 5). Overall rates of gastrointestinal disorders; respiratory, thoracic, and mediastinal disorders; and nervous system disorders were 10% or more lower with subcutaneous than with intravenous bortezomib, as were rates of diarrhoea and peripheral sensory neuropathy (tables 4 and 5).

Rates of peripheral neuropathy events of any grade, and of grade 2 and 3 severity, were lower with subcutaneous

	Subcutaneous bortezomib (N=147)	Intravenous bortezomib (N=74)
Any peripheral neuropathy AE*	56 (38%)†	39 (53%)
Grade ≥2	35 (24%)‡	30 (41%)
Grade ≥3	9 (6%)§	12 (16%)
Time to onset of peripheral neuropathy (safety population; months [95% CI])	NE (4·7–NE)	4·4 (2·8–NE)
Cumulative dose at first onset of peripheral neuropathy (safety population; mg/m² [95% CI])	41·0 (31·2–NE)	25·1 (18·2–39·4)
Estimated event rate of onset of peripheral neuropathy at cumulative dose of 10·4 mg/m² (consistent with two complete treatment cycles)		
Any grade	5·8%	18·8%
Grade ≥2	1·4%	6·0%
Grade ≥3	0%	1·5%
Estimated event rate of onset of peripheral neuropathy at cumulative dose of 20·8 mg/m² (consistent with four complete treatment cycles)		
Any grade	27·3%	44·0%
Grade ≥2	14·2%	28·0%
Grade ≥3	5·0%	12·1%
Risk factors for peripheral neuropathy		
Grade 1 peripheral neuropathy at baseline	34 (23%)	21 (28%)
Diabetes at baseline	19 (13%)	8 (11%)
Previous exposure to neurotoxic agents	126 (86%)	63 (85%)

Data are number (%) or median (IQR), unless otherwise indicated. AE=adverse event. NE=not estimable. *Medical Dictionary for Regulatory Activities high-level term, including peripheral sensory neuropathy, peripheral motor neuropathy, and neuropathy peripheral. For comparison between intravenous and subcutaneous groups, two-sided Fisher's exact test: †p=0·044; ‡p=0·012; §p=0·026.

Table 6: **Rates of peripheral neuropathy events and risk factors by treatment group**

than with intravenous administration (table 6); most peripheral neuropathy events were peripheral sensory neuropathies (table 5). Risk factors for peripheral neuropathy were balanced between groups (table 6); in patients with pre-existing grade 1 peripheral neuropathy, ten of 34 (29%) subcutaneous patients and nine of 21 (43%) intravenous patients developed grade 2 peripheral neuropathy, and three (9%) and five (24%) developed grade 3 peripheral neuropathy, respectively. 48 of 78 (62%) peripheral neuropathy events in the subcutaneous group and 35 of 52 (67%) in the intravenous group have to date resolved or improved in a median of 2·8 months (IQR 1·1–6·1) and 1·5 months (0·8–4·7), respectively.

Nine of 147 (6%) patients had one or more subcutaneous injection-site reaction reported as an adverse event, which resulted in a bortezomib dose modification in two (1%) patients (discontinuation or dose withholding). From the investigator-reported local injection-site questionnaire, the most common reaction was redness (84 of 147 [57%] patients). Two of 147 (1%) patients in the subcutaneous group had severe injection-site reactions. All reactions resolved completely in a median of 6 days (range 1–73).

32 patients (18 in subcutaneous group, 14 in intravenous group) from eight centres enrolled in the pharmacokinetic and pharmacodynamic substudy. Figure 3 shows mean bortezomib plasma concentration–time profiles after subcutaneous and intravenous administration on day 11, cycle 1. Mean maximum plasma concentration (C_{max}) was ten times lower after subcutaneous than intravenous injection with a longer median time to C_{max} (T_{max}) of 0·5 h; mean bortezomib systemic exposure (AUC_{last}) was similar between subcutaneous injection and intravenous administration (table 7). Mean percentage inhibition of 20S proteasome activity (E_{max}) and area under the effect-time curve (mean AUE_{72}) were also similar between administration routes; time to maximum percentage inhibition of 20S proteasome activity was longer after

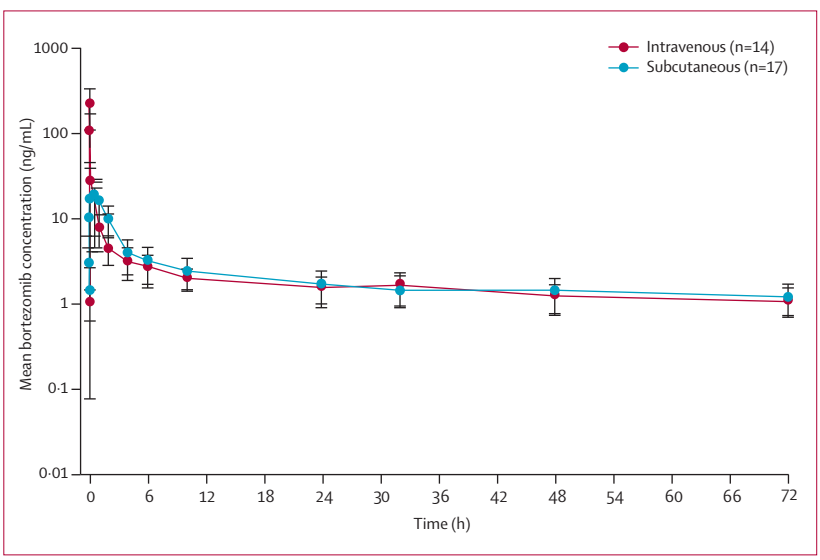

Figure 3: **Plasma concentration–time profiles for subcutaneous and intravenous administration of bortezomib**

Blood samples were collected in cycle 1 on day 1 before the dose; on day 11 immediately before dosing; at 2, 5, 15, and 30 min; and 1, 2, 4, 6, 10, 24 h (day 12), 32 h (day 12), 48 h (day 13), and 72 h (day 14) after dosing. One patient in the subcutaneous group was randomly assigned but discontinued before start of treatment and therefore was excluded from this substudy. Error bars show SDs.

	Subcutaneous bortezomib (n=17*)	Intravenous bortezomib (n=14)
Pharmacokinetics		
C_{max} (ng/mL)	20·4 (8·87)	223 (101)
T_{max} (min)	30 (5–60)	2 (2–5)
AUC_{last} (ng×h/mL)	155 (56·8)	151 (42·9)
Pharmacodynamics		
E_{max} (%)	63·7% (10·6)	69·3% (13·2)
T_{Emax} (min)	120 (30–1440)	5 (2–30)
AUE_{72} (%×h)	1714 (617)	1383 (767)

Data are mean (SD) or median (range). C_{max}=maximum plasma concentration. T_{max}=time to C_{max}. AUC_{last}=area under the concentration–time curve from time 0 to the last timepoint at which bortezomib was quantifiable. E_{max}=observed maximum percentage inhibition of 20S proteasome activity. T_{Emax}=time to E_{max}. AUE_{72}=area under the percentage inhibition–time curve from time 0–72 h. *One patient in the subcutaneous group was randomly assigned but discontinued before start of treatment and therefore was excluded from the substudy.

Table 7: **Pharmacokinetic and pharmacodynamic parameters by route of administration**

subcutaneous than intravenous administration (table 7). We recorded no differences in pharmacokinetic or pharmacodynamic parameters related to the site of subcutaneous injection (data not shown). Patients' levels of subcutaneous fat did not seem to affect overall systemic exposure, as suggested by the equivalent AUC_{last} between the subcutaneous and intravenous groups, and did not seem to substantially affect bortezomib absorption, as suggested by the median T_{max} of 0·5 h (range 0·08–1·00) in patients in the subcutaneous group in the pharmacokinetic substudy (table 7).

Discussion

This multicentre, randomised phase 3 study in patients with relapsed multiple myeloma clearly showed that subcutaneous bortezomib was non-inferior in terms of efficacy compared with intravenous administration. We recorded similarity between groups across all efficacy endpoints, including rates of CR, near CR, and very good PR after four cycles; response rates after eight cycles, including the addition of dexamethasone; M-protein changes; time to response; duration of response; and other time-to-event endpoints.

This non-inferior efficacy might be expected on the basis of the findings of the pharmacokinetic and pharmacodynamic analyses. Although, as would be expected, C_{max} was lower and T_{max} longer with subcutaneous than with intravenous administration, bortezomib systemic exposure was equivalent between groups. Similarly, although time to E_{max} for maximum proteasome inhibition was longer with subcutaneous administration, overall AUE_{72} was similar in both groups. These findings are consistent with those reported from the phase 1 study.[17] Additionally, our findings show that the pharmacokinetics and pharmacodynamics of subcutaneous administration of bortezomib were not affected by the higher injection concentration used in our study than that in the phase 1 trial (2·5 mg/mL *vs* 1 mg/mL).

The efficacy of bortezomib in both groups seemed to be similar to or better than that in previous phase 3 studies investigating single-agent bortezomib in relapsed multiple myeloma.[8–10] In 278 patients with KPS 70% or greater and one to three previous lines of therapy in the APEX study,[8,9] and in 310 patients with KPS 70% or greater in the MMY-3001 study,[10] ORRs after four cycles of single-agent intravenous bortezomib were 41% and 38%, respectively, compared with 42% in our study. Median time to progression was 6·2 months in APEX and 6·5 months in MMY-3001,[8–10] compared with 9·4 months or 10·4 months reported in our study. Our patient population included more second-line patients than did the APEX study, which is consistent with bortezomib being used more frequently in earlier disease settings than in older studies. This difference could have contributed to the numerically longer time to progression, together with greater bortezomib exposure or cumulative dose. Additionally, this apparent efficacy increase could have been associated with addition of dexamethasone to treatment after four cycles, which occurred in about 50% of patients.

About a quarter of patients who received dexamethasone in addition to bortezomib had an improvement in response from cycle 4 to cycle 8. This finding accords with previous results showing improved responses with addition of dexamethasone to bortezomib.[13,14,24,25] In view of the similar eligibility criteria used for our study compared with previous phase 3 studies of single-agent bortezomib, the study populations having similar characteristics to the overall myeloma population, and the inclusion of patients from several countries with different diagnosis and treatment access, the findings of our study seem to be applicable to the overall population of patients with myeloma and across different health-care settings.

This study provides important findings about the toxic effects of bortezomib in the subcutaneous group. Subcutaneous administration had acceptable local tolerability. Local reactions consisted mainly of reversible redness and infrequently led to reporting of an adverse event or dose modifications. Overall, subcutaneous administration seemed to have an improved systemic safety profile compared with intravenous delivery, with lower rates of grade 3 or worse adverse events, and fewer bortezomib dose reductions and discontinuations because of adverse events. A potential limitation of our study is that no patient-reported outcome or health-related quality-of-life data were collected; such data could have been useful to differentiate the administrative approaches in addition to the differing systemic safety profiles, and to reflect the increased convenience of subcutaneous administration.

Peripheral neuropathy is a well known and important side-effect of bortezomib.[26] Notably, we recorded

Panel: Research in context

Systematic review

The standard route of administration of the proteasome inhibitor bortezomib is by intravenous injection. At the time of the design of this study, results from a phase 1 study in patients with relapsed multiple myeloma were available and suggested that the systemic exposure and pharmacodynamics, and the efficacy and safety, of subcutaneous bortezomib seemed to be similar to that of intravenous bortezomib; subcutaneous delivery of bortezomib had not been previously investigated in a large, randomised phase 3 study. Thus we designed this study for the further exploration of subcutaneous administration as an alternative route of delivery of bortezomib in a larger patient population.

Interpretation

The findings of our study show that subcutaneous administration of bortezomib is non-inferior to intravenous injection and offers similar efficacy across all endpoints. Furthermore, results from our study suggest that subcutaneous administration seems to have an improved systemic safety profile compared with intravenous delivery, notably resulting in significantly lower rates of peripheral neuropathy, which is an important side-effect of bortezomib. To our knowledge, this is the first report of an improved safety profile with subcutaneous versus intravenous bortezomib, and these findings could thus increase the use of bortezomib in the treatment of multiple myeloma, with subcutaneous injection representing a promising alternative to standard intravenous administration.

significantly lower rates of peripheral neuropathy of all grades, grade 2 and higher, and grade 3 and higher with subcutaneous bortezomib than with intravenous bortezomib, despite similar rates of potential risk factors in each group. Within the intensive twice per week schedule used in this study, this lower rate of peripheral neuropathy with subcutaneous dosing might be attributable to several factors, including the lower C_{max}, although the small number of patients with pharmacokinetic data and peripheral neuropathy adverse events preclude any conclusions about correlations. However, because lower rates of peripheral neuropathy have also been recorded with bortezomib 1·3 mg/m² or 1·6 mg/m² on a once per week schedule,[27,28] lower C_{max} is unlikely to be the only potential explanation for the decrease in peripheral neuropathy. Further analysis is warranted.

Subcutaneous administration seems to provide an additional option to reduce bortezomib-related peripheral neuropathy, and in conjunction with dosing or schedule modifications[27,28] could further reduce neuropathy side-effects to a level such that potential peripheral neuropathy risk factors no longer constitute a limiting factor for selection of bortezomib treatment. The increased convenience of subcutaneous administration might also be relevant for investigation in settings such as maintenance therapy. This new route of administration could favour home administration of the drug, with substantial cost reduction and greatly improved patient convenience.

In conclusion, this phase 3 study showed that subcutaneous administration of bortezomib is non-inferior to the standard intravenous route of delivery in patients with relapsed multiple myeloma and seems to have an improved systemic safety profile (panel). Subcutaneous administration is a promising alternative to intravenous administration, particularly in patients with poor venous access or at increased risk of side-effects.

Contributors

PM, D-LE, HvdV, WD, and J-LH designed the study. PM, HP, SGr, IK, XL, MG, GR, ZM, TR, AS, BA, MK, JC, and J-LH recruited and treated patients for this study. PM, HP, SGr, IK, XL, MG, GR, ZM, TR, AS, BA, MK, JC, HF, SGi, HvdV, WD, and J-LH collected and collated data. HF, SGi, HvdV, and WD did statistical analyses. PM, HvdV, and WD interpreted the data. PM, HvdV, and WD wrote the first draft of the report. All authors reviewed the draft report, provided critical feedback, and reviewed and approved the final version.

Conflicts of interest

PM is an advisory board member for and has received honoraria from Janssen/Millennium Pharmaceuticals. SGr has received honoraria from Janssen. XL has received institutional grants and lecture fees from Janssen. JC has received institutional grants for research studies involving bortezomib, and speaker or chair fees for educational meetings sponsored by Ortho-Biotech. D-LE is an employee of Millennium Pharmaceuticals, and owns stock in Johnson & Johnson. HF, SGi, HvdV, and WD are employees of Janssen Research and Development (Johnson & Johnson Pharmaceutical Research and Development); and SGi, HvdV, and WD own stock in Janssen Research and Development (Johnson & Johnson). J-LH has received honoraria, payment for development of educational presentations including service on speakers' bureaus, and travel or accommodation expenses from Janssen and Celgene. HP, IK, MG, GR, ZM, TR, AS, BA, MK declare that they have no conflicts of interest.

Acknowledgments

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VELCADE safely and effectively. See full prescribing information for VELCADE.

VELCADE® (bortezomib) for Injection
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Dosage and Administration	
Management of Peripheral Neuropathy (2.5)	1/2012
Administration Precautions (2.7)	1/2012
Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)	1/2012
Warnings and Precautions, Peripheral Neuropathy (5.1)	1/2012

----------INDICATIONS AND USAGE----------

VELCADE is a proteasome inhibitor indicated for:

- treatment of patients with multiple myeloma (1.1)
- treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy (1.2)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose of VELCADE is 1.3 mg/m^2 administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. (2.1, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 1 single-use vial contains 3.5 mg of bortezomib. Dose must be individualized to prevent overdose. (3)

----------CONTRAINDICATIONS----------

- VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. (4)
- VELCADE is contraindicated for intrathecal administration. (4)

----------WARNINGS AND PRECAUTIONS----------

- Peripheral neuropathy, including severe cases, may occur - manage with dose modification or discontinuation. (2.5) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.5, 5.1)
- Hypotension can occur. Use caution when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated. (5.2)
- Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Acute diffuse infiltrative pulmonary disease has been reported. (5.4)
- Nausea, diarrhea, constipation, and vomiting have occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia or neutropenia can occur; complete blood counts should be regularly monitored throughout treatment. (5.7)
- Tumor Lysis Syndrome (5.8), Reversible Posterior Leukoencephalopathy Syndrome (5.5), and acute hepatic failure (5.9) have been reported.
- Women should avoid becoming pregnant while being treated with VELCADE. Pregnant women should be apprised of the potential harm to the fetus. (5.11, 8.1)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (incidence ≥ 30%) in clinical studies include asthenic conditions, diarrhea, nausea, constipation, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia and decreased appetite, neutropenia, neuralgia, leukopenia and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Millennium Pharmaceuticals at 1-866 VELCADE or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors. (7.1)
- Concomitant use of strong CYP3A4 inducers is not recommended. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication. (8.8)
- Hepatic Impairment: Use a lower starting dose for patients with moderate or severe hepatic impairment. (2.6, 5.10, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [1/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma.

1.2 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.

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of VELCADE is 1.3 mg/m^2. VELCADE may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]. When administered intravenously, VELCADE is administered as a 3 to 5 second bolus intravenous injection. VELCADE is for intravenous or subcutaneous use only. VELCADE should not be administered by any other route.

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

2.1 Dosage in Previously Untreated Multiple Myeloma

VELCADE (bortezomib) for Injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1. 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 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice Weekly VELCADE (Cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (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
Melphalan(9 mg/m^2) Prednisone(60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly VELCADE (Cycles 5-9 when used in combination with Melphalan and Prednisone)

Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan(9 mg/m^2) Prednisone(60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

2.2 Dose Modification Guidelines for Combination Therapy with VELCADE, Melphalan and Prednisone

Prior to initiating any cycle of therapy with VELCADE in combination with melphalan and prednisone:

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

Table 2: Dose Modifications during Cycles of Combination VELCADE, Melphalan and Prednisone Therapy

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 is not above 30×10^9/L or ANC is not above 0.75×10^9/L on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
If several VELCADE doses in consecutive cycles are withheld due to toxicity	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 or higher 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 or modify VELCADE as outlined in Table 3.

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

For dose modifications guidelines for peripheral neuropathy see Management of Peripheral Neuropathy section (2.5).

2.3 Dosage in Relapsed Multiple Myeloma and Mantle Cell Lymphoma

VELCADE (1.3 mg/m^2/dose) is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, VELCADE may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) [*see Clinical Studies section (14) for a description of dose administration during the trials*]. At least 72 hours should elapse between consecutive doses of VELCADE.

2.4 Dose Modification Guidelines for Relapsed Multiple Myeloma and Mantle Cell Lymphoma

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 Warnings and Precautions (5)*]. 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 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

For dose modifications guidelines for peripheral neuropathy see Management of Peripheral Neuropathy section (2.5).

2.5 Management of Peripheral Neuropathy

Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience VELCADE-related neuropathic pain and/or peripheral neuropathy see Table 3.

Table 3: 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 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce VELCADE to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL ***)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue VELCADE

*Grading based on NCI Common Terminology Criteria CTCAE v4.0

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

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

2.6 Dosage in 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. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see Table 4). [*see Warnings and Precautions (5.10), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*]

Table 4: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	Less than or equal to 1.0x ULN	More than ULN	None
	More than 1.0x–1.5x ULN	Any	None
Moderate	More than 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	More than 3x ULN	Any	

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

2.7 Administration Precautions

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)* and follow reconstitution instructions for 1 mg/mL]. Alternatively, the intravenous route of administration should be considered [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]

VELCADE is an antineoplastic. Procedures for proper handling and disposal should be considered. [*see How Supplied/Storage and Handling (16)*]

In clinical trials of VELCADE intravenous, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

2.8 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Proper aseptic technique should be used. Reconstitute **only with 0.9% sodium chloride**. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). **Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered** [*see Administration Precautions (2.7)*]

For each 3.5 mg single-use vial of bortezomib reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 5):

Table 5: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted VELCADE to be administered:

- **Intravenous Administration [1 mg/mL concentration**]

$$\frac{\text{VELCADE dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{1 mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

- **Subcutaneous Administration [2.5 mg/mL concentration]**

$$\frac{\text{VELCADE dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{2.5 mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

Stickers that indicate the route of administration are provided with each VELCADE vial. These stickers should be placed directly on the syringe of VELCADE once VELCADE is prepared to help alert practitioners of the correct route of administration for VELCADE.

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.

Stability: Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light.

VELCADE contains no antimicrobial preservative. Reconstituted VELCADE should be administered within 8 hours of preparation. When reconstituted as directed, VELCADE may be stored at 25ºC (77ºF). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

3 DOSAGE FORMS AND STRENGTHS

Each single-use vial of VELCADE contains 3.5 mg of bortezomib as a sterile lyophilized powder.

4 CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

5 WARNINGS AND PRECAUTIONS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE.

5.1 Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor 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 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs. intravenous the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for subcutaneous and 41% for intravenous. Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 16% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may benefit from a decrease in the dose and/or a less dose-intense schedule [*see Dosage and Administration (2.5)*]. In the single agent phase 3 relapsed multiple myeloma study of VELCADE vs. Dexamethasone following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the relapsed multiple myeloma study. 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 [*see Adverse Reactions (6)*]. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 **Hypotension**

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%. 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, and administration of mineralocorticoids and/or sympathomimetics [*see Adverse Reactions (6)*].

5.3 **Cardiac Disorders**

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE vs. dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) 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.

5.4 **Pulmonary Disorders**

There have been 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.

In a clinical trial, the first 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.

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.

5.5 **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

There have been reports of RPLS in patients receiving VELCADE. RPLS 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 RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known.

5.6 **Gastrointestinal Adverse Events**

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting [*see Adverse Reactions (6)*] sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration.

5.7 **Thrombocytopenia/Neutropenia**

VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in Table 6. In the relapsed multiple myeloma study of VELCADE vs. dexamethasone, the incidence of significant bleeding events ($\geq$ Grade 3) was similar on both the

VELCADE (4%) and dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE [*see Table 2 and Dosage and Administration (2.4)*]. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may be considered. The incidence of febrile neutropenia was < 1%.

Table 6: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

Pretreatment Platelet Count*	Number of Patients (N=331)**	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 baseline platelet count of 50,000/µL was required for study eligibility
** Data were missing at baseline for 1 patient

5.8 Tumor Lysis Syndrome

Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells, the complications of tumor lysis syndrome may occur. 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.

5.9 Hepatic Events

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.

5.10 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 Dosage and Administration (2.6), Use In Specific Populations (8.7) and Clinical Pharmacology (12.3)*]

5.11 Use in Pregnancy

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses. [*see Use in Specific Populations (8.1)*]

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Peripheral Neuropathy [*see Warnings and Precautions (5.1); Dosage and Administration (2.5)(Table 3)*]
- Hypotension [*see Warnings and Precautions (5.2)*]
- Cardiac Disorders [*see Warnings and Precautions (5.3)*]
- Pulmonary Disorders [*see Warnings and Precautions (5.4)*]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and Precautions (5.5)*]

- Gastrointestinal Adverse Events [*see Warnings and Precautions (5.6)*]
- Thrombocytopenia/Neutropenia [*see Warnings and Precautions (5.7)*]
- Tumor Lysis Syndrome [*see Warnings and Precautions (5.8)*]
- Hepatic Events [*see Warnings and Precautions (5.9)*]

6.1 **Clinical Trials Safety Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

***Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma*:**

Table 7 describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE (1.3 mg/m^2) administered intravenously in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective randomized study.

The safety profile of VELCADE in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone.

Table 7: Most Commonly Reported Adverse Events (≥ 10% in VELCADE, Melphalan and Prednisone arm) with Grades 3 and ≥ 4 Intensity in the Previously Untreated Multiple Myeloma Study

	VELCADE, Melphalan and Prednisone (N=340)			**Melphalan and Prednisone** (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	178 (52)	68 (20)	59 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	35 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal Disorders						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Abdominal Pain	49 (14)	7 (2)	0	22 (7)	1 (<1)	0
Abdominal Pain Upper	40 (12)	1 (<1)	0	29 (9)	0	0
Dyspepsia	39 (11)	0	0	23 (7)	0	0
Nervous System Disorders						
Peripheral Neuropathy	159 (47)	43 (13)	2 (1)	18 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0
Headache	49 (14)	2 (1)	0	35 (10)	4 (1)	0
Paresthesia	45 (13)	6 (2)	0	15 (4)	0	0

General Disorders and Administration Site Conditions						
Pyrexia	99 (29)	8 (2)	2 (1)	64 (19)	6 (2)	2 (1)
Fatigue	98 (29)	23 (7)	2 (1)	86 (26)	7 (2)	0
Asthenia	73 (21)	20 (6)	1 (<1)	60 (18)	9 (3)	0
Edema Peripheral	68 (20)	2 (1)	0	34 (10)	0	0
Infections and Infestations						
Pneumonia	56 (16)	16 (5)	13 (4)	36 (11)	13 (4)	9 (3)
Herpes Zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Bronchitis	44 (13)	4 (1)	0	27 (8)	4 (1)	0
Nasopharyngitis	39 (11)	1 (<1)	0	27 (8)	0	0
Musculoskeletal and Connective Tissue Disorders						
Back Pain	58 (17)	9 (3)	1 (<1)	62 (18)	11 (3)	1 (<1)
Pain In Extremity	47 (14)	8 (2)	0	32 (9)	3 (1)	1 (<1)
Bone Pain	37 (11)	7 (2)	1 (<1)	35 (10)	7 (2)	0
Arthralgia	36 (11)	4 (1)	0	50 (15)	2 (1)	1 (<1)
Metabolism and Nutrition Disorders						
Anorexia	77 (23)	9 (3)	1 (<1)	34 (10)	4 (1)	0
Hypokalemia	44 (13)	19 (6)	3 (1)	25 (7)	8 (2)	2 (1)
Skin and Subcutaneous Tissue Disorders						
Rash	66 (19)	2 (1)	0	24 (7)	1 (<1)	0
Pruritus	35 (10)	3 (1)	0	18 (5)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	71 (21)	0	0	45 (13)	2 (1)	0
Dyspnea	50 (15)	11 (3)	2 (1)	44 (13)	5 (1)	4 (1)
Psychiatric Disorders						
Insomnia	69 (20)	1 (<1)	0	43 (13)	0	0
Vascular Disorders						
Hypertension	45 (13)	8 (2)	1 (<1)	25 (7)	2 (1)	0
Hypotension	41 (12)	4 (1)	3 (1)	10 (3)	2 (1)	2 (1)

Relapsed Multiple Myeloma Randomized Study of VELCADE vs. Dexamethasone

The safety data described below and in Table 8 reflect exposure to either VELCADE (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. VELCADE was administered intravenously at doses of 1.3 mg/m^2 twice weekly for 2 out of 3 weeks (21 day cycle). After eight 21-day cycles patients continued therapy for three 35-day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (9 months) with a median duration of 6 cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and 1 to 3 prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall frequency of adverse events was similar in men and women, and in patients < 65 and ≥ 65 years of age. Most patients were Caucasian. [*see Clinical Studies (14.1)*]

Among the 331 VELCADE-treated patients, the most commonly reported events overall were asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%), peripheral neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric disorders (each 35%), anorexia and appetite decreased (34%), paresthesia and dysesthesia (27%), anemia and headache (each 26%), and cough (21%). The most commonly reported adverse events reported among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung infections (each 21%). Fourteen percent (14%) of patients in the VELCADE treated arm experienced a Grade 4 adverse event; the most common toxicities were thrombocytopenia (4%), neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%) of dexamethasone treated patients experienced a Grade 4 adverse event; the most common toxicity was hyperglycemia (2%).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

Serious adverse events are defined as any event, regardless of causality, that results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability, or is deemed to be an important medical event. A total of 144 (44%) patients from the VELCADE treatment arm experienced an SAE during the study, as did 144 (43%) dexamethasone-treated patients. The most commonly reported SAEs in the VELCADE treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting (3%). In the dexamethasone treatment group, the most commonly reported SAEs were pneumonia (7%), pyrexia (4%), and hyperglycemia (3%).

A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment group and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from treatment due to adverse events assessed as drug-related by the investigators. Among the 331 VELCADE treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone group, the most commonly reported drug-related events leading to treatment discontinuation were psychotic disorder and hyperglycemia (2% each).

Four deaths were considered to be VELCADE related in this relapsed multiple myeloma study: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of bacterial meningitis, and 1 case of sudden death at home.

Most Commonly Reported Adverse Events in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

The most common adverse events from the relapsed multiple myeloma study are shown in Table 8. All adverse events with incidence ≥ 10% in the VELCADE arm are included.

Table 8: Most Commonly Reported Adverse Events (≥ 10% in VELCADE arm), with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone (N=663)

	Treatment Group					
	VELCADE (n=331) [n (%)]			Dexamethasone (n=332) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events	All Events	Grade 3 Events	Grade 4 Events
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	26 (8)	3 (<1)
Anorexia and appetite decreased	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Paresthesia and dysesthesia	91 (27)	6 (2)	0	38 (11)	1 (<1)	0
Anemia	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Headache	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Lower respiratory/ lung infections	48 (15)	12 (4)	2 (<1)	69 (21)	24 (7)	1 (<1)
Pain in limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Back pain	46 (14)	10 (3)	0	33 (10)	4 (1)	0
Arthralgia	45 (14)	3 (<1)	0	35 (11)	5 (2)	0
Dizziness (excl. vertigo)	45 (14)	3 (<1)	0	34 (10)	0	0
Nasopharyngitis	45 (14)	1 (<1)	0	22 (7)	0	0
Herpes zoster	42 (13)	6 (2)	0	15 (5)	4 (1)	1 (<1)
Muscle cramps	41 (12)	0	0	50 (15)	3 (<1)	0
Myalgia	39 (12)	1 (<1)	0	18 (5)	1 (<1)	0
Rigors	37 (11)	0	0	8 (2)	0	0
Edema lower limb	35 (11)	0	0	43 (13)	1 (<1)	0

Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

In the phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. These patients were treated for a total of 5.3 to 23 months, including time on VELCADE in the prior VELCADE study. [*see Clinical Studies (14)*]

Safety Experience from the Phase 3 Open-Label Study of VELCADE Subcutaneous vs. Intravenous in Relapsed Multiple Myeloma

The safety and efficacy of VELCADE administered subcutaneously 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 subcutaneous vs. intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in Table 9 reflect exposure to either VELCADE subcutaneous (n=147) or VELCADE intravenous (n=74) [*see Clinical Studies (14.1)*]

Table 9: Most Commonly Reported Adverse Events (≥ 10%), with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of VELCADE Subcutaneous vs. Intravenous

	Subcutaneous (N=147)[a]			Intravenous (N=74)[a]		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
MedDRA Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	53 (36)	14 (10)	4 (3)	26 (35)	6 (8)	0
Leukopenia	29 (20)	9 (6)	0	16 (22)	4 (5)	1 (1)
Neutropenia	42 (29)	22 (15)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	52 (35)	12 (8)	7 (5)	27 (36)	8 (11)	6 (8)
Gastrointestinal disorders						
Abdominal pain	5 (3)	1 (1)	0	8 (11)	0	0
Abdominal pain upper	3 (2)	0	0	8 (11)	0	0
Constipation	21 (14)	1 (1)	0	11 (15)	1 (1)	0
Diarrhea	35 (24)	2 (1)	1 (1)	27 (36)	3 (4)	1 (1)
Nausea	27 (18)	0	0	14 (19)	0	0
Vomiting	17 (12)	3 (2)	0	12 (16)	0	1 (1)
General disorders and administration site conditions						
Asthenia	23 (16)	3 (2)	0	14 (19)	4 (5)	0
Fatigue	17 (12)	3 (2)	0	15 (20)	3 (4)	0
Pyrexia	28 (19)	0	0	12 (16)	0	0
Infections and infestations						
Herpes zoster	16 (11)	2 (1)	0	7 (9)	1 (1)	0
Investigations						
Weight decreased	22 (15)	0	0	2 (3)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	14 (10)	0	0	7 (9)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	21 (14)	1 (1)	0	8 (11)	1 (1)	1 (1)
Pain in extremity	8 (5)	1 (1)	0	8 (11)	2 (3)	0
Nervous system disorders						
Headache	5 (3)	0	0	8 (11)	0	0
Neuralgia	35 (24)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies NEC[b]	56 (38)	8 (5)	1 (1)	39 (53)	11 (15)	1 (1)
Psychiatric disorders						
Insomnia	18 (12)	0	0	8 (11)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	11 (7)	2 (1)	0	9 (12)	2 (3)	0
Vascular disorders						
Hypertension	14 (10)	3 (2)	0	3 (4)	0	0

[a] Safety population: 147 patients in the subcutaneous treatment and 74 patients in the intravenous treatment who received at least 1 dose of study medication

[b] Represents MedDRA high level term

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥ 3 adverse events. Differences of ≥ 5% were reported in neuralgia (3%

subcutaneous vs. 9% intravenous), peripheral neuropathy (6% subcutaneous vs. 16% intravenous), and thrombocytopenia (13% subcutaneous vs. 19% intravenous).

A local reaction was reported in 6% of patients in the subcutaneous group as an adverse event, mostly redness. Only 2 (1%) patients were reported as having severe reactions, 1 case of pruritus and 1 case of redness. Local reactions led to reduction in injection concentration in one patient and drug discontinuation in one patient. Local reaction events resolved in a median of 6 days.

Dose reductions occurred due to drug related adverse events in 31% of patients in the subcutaneous treatment group compared with 43% of the intravenously treated patients. The most common adverse events leading to a dose reduction included peripheral sensory neuropathy (17% in the subcutaneous treatment group compared with 31% in the intravenous treatment group); and neuralgia (11% in the subcutaneous treatment group compared with 19% in the intravenous treatment group).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs. Intravenous

The incidence of serious adverse events was similar for the subcutaneous treatment group (36%) and the intravenous treatment group (35%). The most commonly reported SAEs in the subcutaneous treatment arm were pneumonia (6%) and pyrexia (3%). In the intravenous treatment group, the most commonly reported SAEs were pneumonia (7%), diarrhea (4%), peripheral sensory neuropathy (3%) and renal failure (3%).

In the subcutaneous treatment group, 27 patients (18%) discontinued study treatment due to a drug related adverse event compared with 17 patients (23%) in the intravenous treatment group. Among the 147 subcutaneously treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral sensory neuropathy (5%) and neuralgia (5%). Among the 74 patients in the intravenous treatment group, the most commonly reported drug-related events leading to treatment discontinuation were peripheral sensory neuropathy (9%) and neuralgia (9%).

Two patients (1%) in the subcutaneous treatment group and 1 (1%) patient in the intravenous treatment group died due to a drug-related adverse event during treatment. In the subcutaneous group the causes of death were one case of pneumonia and one of sudden death. In the intravenous group the cause of death was coronary artery insufficiency.

Integrated Summary of Safety (Relapsed Multiple Myeloma and Mantle Cell Lymphoma)

Safety data from phase 2 and 3 studies of single agent VELCADE 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously treated multiple myeloma (N=1008) and previously treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 Open-Label Study of VELCADE subcutaneous vs. intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma. [*see Clinical Studies (14)*]

In the integrated analysis, the most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia) (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty percent (20%) of patients experienced at least 1 episode of ≥ Grade 4 toxicity, most commonly thrombocytopenia (5%) and neutropenia (3%).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Integrated Summary of Safety

A total of 50% of patients experienced SAEs during the studies. The most commonly reported SAEs included pneumonia (7%), pyrexia (6%), diarrhea (5%), vomiting (4%), and nausea, dehydration, dyspnea and thrombocytopenia (each 3%).

Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), asthenic conditions (3%) and thrombocytopenia and diarrhea (each 2%).

In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis.

Most Commonly Reported Adverse Events in the Integrated Summary of Safety

The most common adverse events are shown in Table 10. All adverse events occurring at ≥ 10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse reactions that follows.

Table 10: Most Commonly Reported (≥ 10% Overall) Adverse Events in Integrated Analyses of Relapsed Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m^2 Dose (N=1163)

	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
Adverse Events	**All Events**	**≥ Grade 3**	**All Events**	**≥ Grade 3**	**All Events**	**≥ Grade 3**
Asthenic conditions	740 (64)	189 (16)	628 (62)	160 (16)	112 (72)	29 (19)
Nausea	640 (55)	43 (4)	572 (57)	39 (4)	68 (44)	4 (3)
Diarrhea	604 (52)	96 (8)	531 (53)	85 (8)	73 (47)	11 (7)
Constipation	481 (41)	26 (2)	404 (40)	22 (2)	77 (50)	4 (3)
Peripheral neuropathy	457 (39)	134 (12)	372 (37)	114 (11)	85 (55)	20 (13)
Thrombocytopenia	421 (36)	337 (29)	388 (38)	320 (32)	33 (21)	17 (11)
Appetite decreased	417 (36)	30 (3)	357 (35)	25 (2)	60 (39)	5 (3)
Pyrexia	401 (34)	36 (3)	371 (37)	34 (3)	30 (19)	2 (1)
Vomiting	385 (33)	57 (5)	343 (34)	53 (5)	42 (27)	4 (3)
Anemia	333 (29)	124 (11)	306 (30)	120 (12)	27 (17)	4 (3)
Edema	262 (23)	10 (<1)	218 (22)	6 (<1)	44 (28)	4 (3)
Paresthesia and dysesthesia	254 (22)	16 (1)	240 (24)	14 (1)	14 (9)	2 (1)
Headache	253 (22)	17 (1)	227 (23)	17 (2)	26 (17)	0
Dyspnea	244 (21)	59 (5)	209 (21)	52 (5)	35 (23)	7 (5)
Cough	232 (20)	5 (<1)	202 (20)	5 (<1)	30 (19)	0
Insomnia	232 (20)	7 (<1)	199 (20)	6 (<1)	33 (21)	1 (<1)
Rash	213 (18)	10 (<1)	170 (17)	6 (<1)	43 (28)	4 (3)
Arthralgia	199 (17)	27 (2)	179 (18)	25 (2)	20 (13)	2 (1)
Neutropenia	195 (17)	143 (12)	185 (18)	137 (14)	10 (6)	6 (4)
Dizziness (excluding vertigo)	195 (17)	18 (2)	159 (16)	13 (1)	36 (23)	5 (3)
Pain in limb	179 (15)	36 (3)	172 (17)	36 (4)	7 (5)	0
Abdominal pain	170 (15)	30 (3)	146 (14)	22 (2)	24 (15)	8 (5)
Bone pain	166 (14)	37 (3)	163 (16)	37 (4)	3 (2)	0
Back pain	151 (13)	39 (3)	150 (15)	39 (4)	1 (<1)	0
Hypotension	147 (13)	37 (3)	124 (12)	32 (3)	23 (15)	5 (3)
Herpes zoster	145 (12)	22 (2)	131 (13)	21 (2)	14 (9)	1 (<1)
Nasopharyngitis	139 (12)	2 (<1)	126 (13)	2 (<1)	13 (8)	0
Upper respiratory tract infection	138 (12)	2 (<1)	114 (11)	1 (<1)	24 (15)	1 (<1)
Myalgia	136 (12)	9 (<1)	121 (12)	9 (<1)	15 (10)	0
Pneumonia	134 (12)	72 (6)	120 (12)	65 (6)	14 (9)	7 (5)
Muscle cramps	125 (11)	1 (<1)	118 (12)	1 (<1)	7 (5)	0
Dehydration	120 (10)	40 (3)	109 (11)	33 (3)	11 (7)	7 (5)
Anxiety	118 (10)	6 (<1)	111 (11)	6 (<1)	7 (5)	0

Description of Selected Adverse Events from the Integrated Phase 2 and 3 Relapsed Multiple Myeloma and Phase 2 Mantle Cell Lymphoma Studies

Gastrointestinal Events

A total of 87% of patients experienced at least one GI disorder. The most common GI disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders included dyspepsia and dysgeusia. Grade 3 GI events occurred in 18% of patients; Grade 4 events were 1%. GI events were considered serious in 11% of patients. Five percent (5%) of patients discontinued due to a GI event. Nausea was reported more often in patients with multiple myeloma (57%) compared to patients with mantle cell lymphoma (44%). [*see Warnings and Precautions (5.6)*]

Thrombocytopenia

Across the studies, VELCADE associated thrombocytopenia was characterized by a decrease in platelet count during the dosing period (days 1 to 11) and a return toward baseline during the 10-day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 36% of patients. Thrombocytopenia was Grade 3 in 24%, ≥ Grade 4 in 5%, and serious in 3% of patients, and the event resulted in VELCADE discontinuation in 2% of patients [*see Warnings and Precautions (5.7)*]. Thrombocytopenia was reported more often in patients with multiple myeloma (38%) compared to patients with mantle cell lymphoma (21%). The incidence of ≥ Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (32%) compared to patients with mantle cell lymphoma (11%). [*see Warnings and Precautions (5.7)*]

Peripheral Neuropathy

Overall, peripheral neuropathy NEC occurred in 39% of patients. Peripheral neuropathy was Grade 3 for 11% of patients and Grade 4 for < 1% of patients. Eight percent (8%) of patients discontinued VELCADE due to peripheral neuropathy. The incidence of peripheral neuropathy was higher among patients with mantle cell lymphoma (55%) compared to patients with multiple myeloma (37%).

In the relapsed multiple myeloma study, among the 87 patients who experienced ≥ Grade 2 peripheral neuropathy, 51% had improved or resolved with a median of 3.5 months from first onset.

Among the patients with peripheral neuropathy in the phase 2 multiple myeloma studies that was Grade 2 and led to discontinuation or was ≥ Grade 3, 73% (24 of 33) reported improvement or resolution following VELCADE dose adjustment, with a median time to improvement of one Grade or more from the last dose of VELCADE of 33 days**.** [*see Warnings and Precautions (5.1)*]

Hypotension

The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 3% and ≥ Grade 4 in < 1%. Three percent (3%) of patients had hypotension reported as an SAE, and 1% discontinued due to hypotension. The incidence of hypotension was similar in patients with multiple myeloma (12%) and those with mantle cell lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal event. Doses of antihypertensive medications may need to be adjusted in patients receiving VELCADE. [*see Warnings and Precautions (5.2)*]

Neutropenia

Neutrophil counts decreased during the VELCADE dosing period (days 1 to 11) and returned toward baseline during the 10-day rest period during each treatment cycle. Overall, neutropenia occurred in 17% of patients and was Grade 3 in 9% of patients and ≥ Grade 4 in 3%. Neutropenia was reported as a serious event in < 1% of patients and < 1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥ Grade 3 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with mantle cell lymphoma (4%). [*see Warnings and Precautions (5.7)*]

Asthenic conditions (Fatigue, Malaise, Weakness)
Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and ≥ Grade 4 in < 1% of patients. Four percent (4%) of patients discontinued treatment due to asthenia. Asthenic conditions were reported in 62% of patients with multiple myeloma and 72% of patients with mantle cell lymphoma.

Pyrexia
Pyrexia (> 38ºC) was reported as an adverse event for 34% of patients. The event was Grade 3 in 3% and ≥ Grade 4 in < 1%. Pyrexia was reported as a serious adverse event in 6% of patients and led to VELCADE discontinuation in < 1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (37%) compared to patients with mantle cell lymphoma (19%). The incidence of ≥ Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in patients with mantle cell lymphoma.

Herpes Virus Infection
Physicians should consider using antiviral prophylaxis in subjects being treated with VELCADE. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with VELCADE (13%) than in the control groups (4-5%). Herpes simplex was seen in 2-8% in subjects treated with VELCADE and 1-5% in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus reactivation in the VELCADE, melphalan and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%). In the postmarketing experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have been reported.

Additional Adverse Events from Clinical Studies

The following clinically important SAEs that are not described above have been reported in clinical trials in patients treated with VELCADE administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and lymphatic system disorders: Disseminated intravascular coagulation, lymphopenia, leukopenia

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia

Ear and labyrinth disorders: Hearing impaired, vertigo

Eye disorders: Diplopia and blurred vision, conjunctival infection, irritation

Gastrointestinal disorders: Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux

General disorders and administration site conditions: Injection site erythema, neuralgia, injection site pain, irritation, phlebitis

Hepatobiliary disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure

Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and infestations: Aspergillosis, bacteremia, urinary tract infection, herpes viral infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection

Injury, poisoning and procedural complications: Catheter related complication, skeletal fracture, subdural hematoma

Metabolism and nutrition disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Nervous system disorders*:* Ataxia, coma, dysarthria, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric disorders*:* Agitation, confusion, mental status change, psychotic disorder, suicidal ideation

Renal and urinary disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative

Respiratory, thoracic and mediastinal disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension

Skin and subcutaneous tissue disorders*:* Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis

Vascular disorders*:* Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide postmarketing experience with VELCADE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: atrioventricular block complete, cardiac tamponade, ischemic colitis, encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular coagulation, hepatitis, acute pancreatitis, acute diffuse infiltrative pulmonary disease, reversible posterior leukoencephalopathy syndrome, toxic epidermal necrolysis, acute febrile neutrophilic dermatosis (Sweet's syndrome), herpes meningoencephalitis, optic neuropathy, blindness and ophthalmic herpes.

7 DRUG INTERACTIONS

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2.

7.1 CYP3A4 inhibitors: Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

7.2 CYP2C19 inhibitors: Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.

7.3 CYP3A4 inducers: Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur.

Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE.

St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided.

7.4 Dexamethasone: Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients.

7.5 Melphalan-Prednisone: Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.11)*]

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 0.05mg/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.

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.

8.3 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of VELCADE in children have not been established.

8.5 Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients ≥ 65 were longer on VELCADE compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤ 50, 51-64 and ≥ 65 years old, respectively. [*see Adverse Reactions (6.1); Clinical Studies (14)*]

No overall differences in safety or effectiveness were observed between patients≥ age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

8.6 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. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after the dialysis procedure. For information concerning dosing of melphalan in patients with renal impairment see manufacturer's prescribing information. [*see Clinical Pharmacology (12.3)*]

8.7 Patients with Hepatic Impairment

The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients. [*see Dosage and Administration (2.6), Warnings and Precautions (5.10), and Pharmacokinetics (12.3)*]

8.8 Patients with Diabetes

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.

10 OVERDOSAGE

There is no known specific antidote for VELCADE overdosage [*see Warnings and Precautions (5) and Dosage and Administration (2)*]. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as 2 times the recommended clinical dose on a mg/m^2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

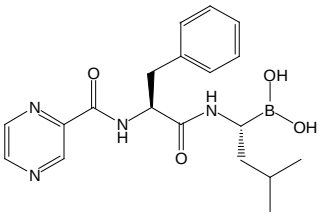
11 DESCRIPTION

VELCADE® (bortezomib) for Injection is an antineoplastic agent available for intravenous injection or subcutaneous use. Each single use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Following twice weekly administration of 1 mg/m^2 and 1.3 mg/m^2 bortezomib doses (n=12 per each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m^2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m^2 and 1.3 mg/m^2 dose regimens, respectively.

12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients (n = 14 for intravenous, n = 17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 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 2 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 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.

Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1 mg/m^2 and 1.3 mg/m^2 showed that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).

Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m^2 doses.

Race: The effect of race on exposure to bortezomib could not be assessed as most of the patients were Caucasian.

Hepatic Impairment: The effect of hepatic impairment (see Table 4 for definition of hepatic impairment) on the pharmacokinetics of bortezomib was assessed in 51 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 Dosage and Administration (2.6), Warnings and Precautions (5.10) and Use in Specific Populations (8.7)*]

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 Use in Specific Populations (8.6)*]

Pediatric: There are no pharmacokinetic data in pediatric patients.

Cytochrome P450**:** Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of > 30μM (> 11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity: Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses ≥ 1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration: In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1-week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma:
A prospective, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether VELCADE administered intravenously (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. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Antiviral prophylaxis was recommended for patients on the VELCADE study arm.

The median age of the patients in the study was 71 years (48;91), 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80 (60;100). Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/L (64;165), and a median platelet count of 221,500 /microliter (33,000;587,000).

Efficacy results for the trial are presented in Table 11. At a pre-specified interim analysis (with median follow-up of 16.3 months), the combination of VELCADE, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was halted, and patients receiving melphalan and prednisone were offered VELCADE in addition. A later, pre-specified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the VELCADE, melphalan and prednisone treatment arm despite subsequent therapies including VELCADE based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the VELCADE, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

Table 11: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	VELCADE, Melphalan and Prednisone n=344	Melphalan and Prednisone n=338
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median[a] (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio[b]	0.54	
(95% CI)	(0.42, 0.70)	
p-value[c]	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)
Median[a] (months)	18.3	14.0
(95% CI)	(16.6, 21.7)	(11.1, 15.0)
Hazard ratio[b]	0.61	
(95% CI)	(0.49, 0.76)	
p-value[c]	0.00001	
Response Rate		
CR[d] n (%)	102 (30)	12 (4)
PR[d] n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR[d] n (%)	238 (69)	115 (34)
p-value[e]	$<10^{-10}$	
Overall Survival at median follow up of 36.7 months		
Events (deaths) n (%)	109 (32)	148 (44)
Median[a] (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio[b]	0.65	
(95% CI)	(0.51, 0.84)	
p-value[c]	0.00084	

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.

[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 VELCADE, melphalan and prednisone

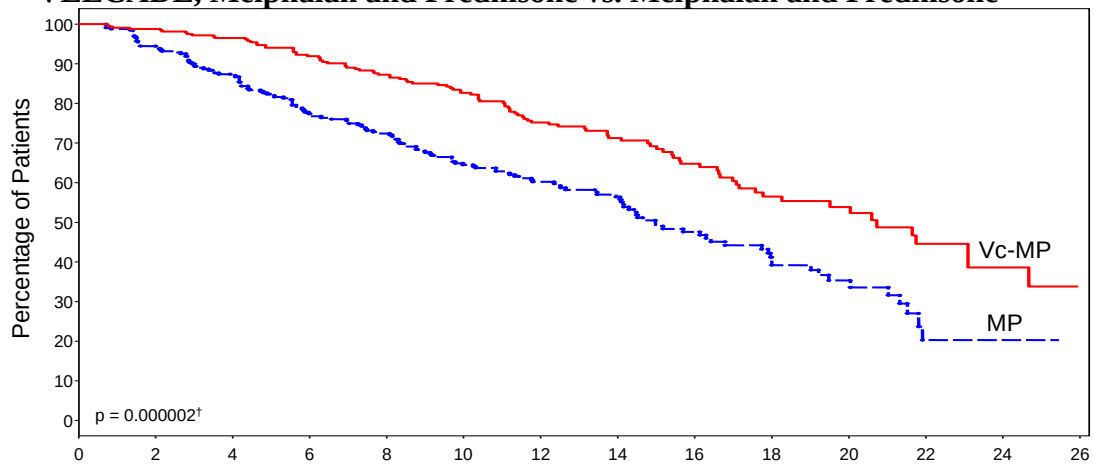
[c] p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region

[d] EBMT criteria

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

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

Figure 1: Time to Progression
VELCADE, Melphalan and Prednisone vs. Melphalan and Prednisone



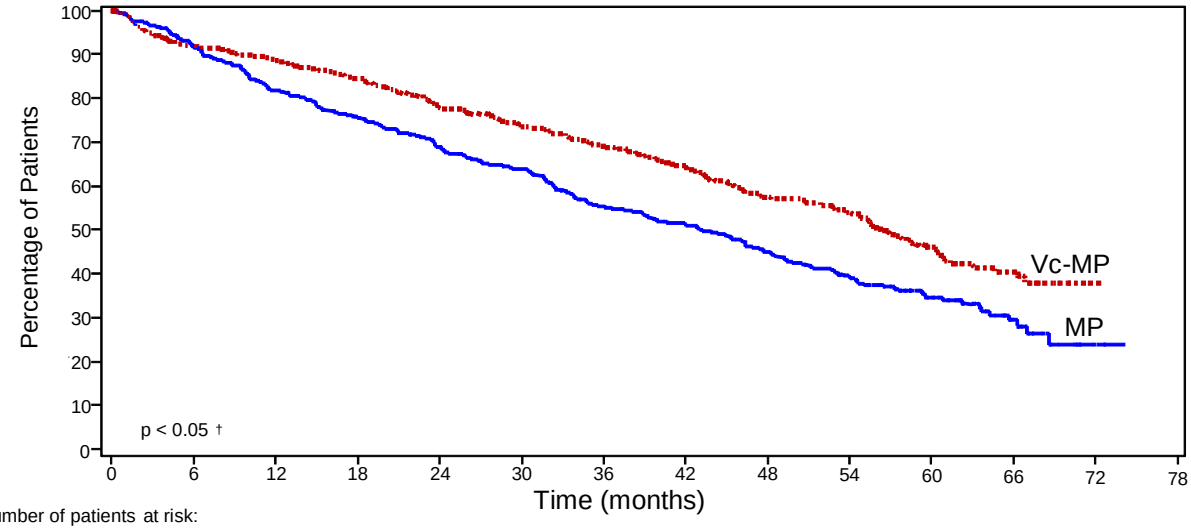
Number of patients at risk:

Vc-MP (n*)	344	309	280	258	240	200	159	114	81	53	35	20	13
MP (n*)	338	298	264	218	200	160	128	90	61	41	20	6	3

* Patients remaining after the indicated timepoint
† p-value from log-rank test

Overall survival was statistically significantly longer on the VELCADE, melphalan and prednisone arm (see Figure 2). (median follow-up 60.1 months)

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



Number of patients at risk:

Vc-MP (n*):	344	300	288	270	246	232	216	199	176	158	78	34	1	0
MP (n*):	338	301	262	240	216	196	168	153	133	112	61	24	3	0

* Patients remaining after the indicated timepoint
† p-value from log-rank test

Randomized, Clinical Study in Relapsed Multiple Myeloma of VELCADE vs. Dexamethasone

A prospective phase 3, international, randomized (1:1), stratified, open-label clinical study 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 12.

Table 12: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

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 β_2-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%
Previous Therapy		
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. Patients achieving a CR were treated for 4 cycles beyond first evidence of CR. Within each 3-week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous 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 intravenous 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 Dosage and Administration (2.1)*]

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 21-35). 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.

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 relapsed multiple myeloma study are presented in Table 13. 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 13: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study

	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	**Dex**	**VELCADE**	**Dex**	**VELCADE**	**Dex**
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=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 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (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)
Hazard ratio [b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
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)
PR [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	

[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

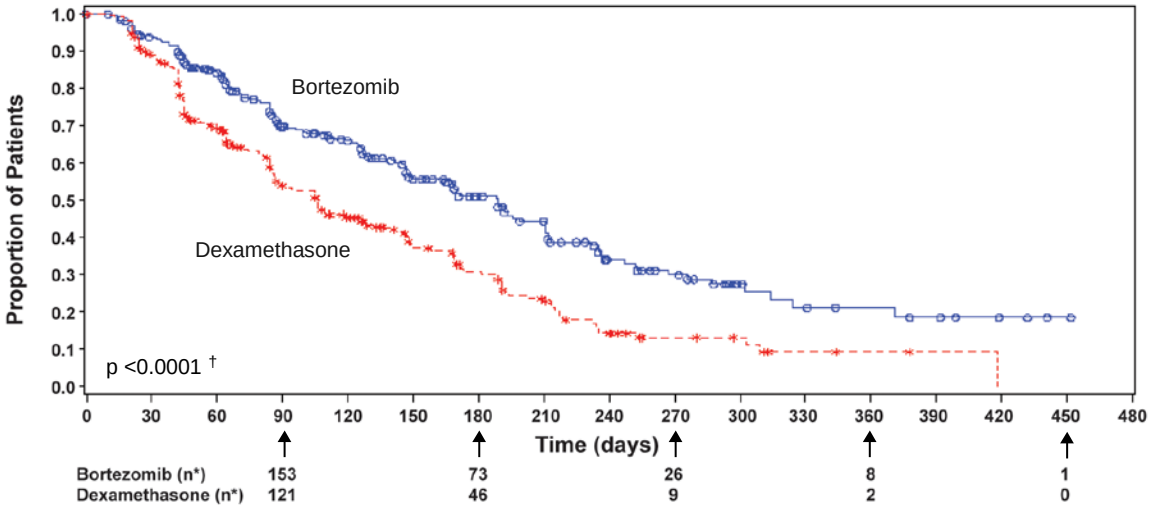
[f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category

[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

TTP was statistically significantly longer on the VELCADE arm (see Figure 3).

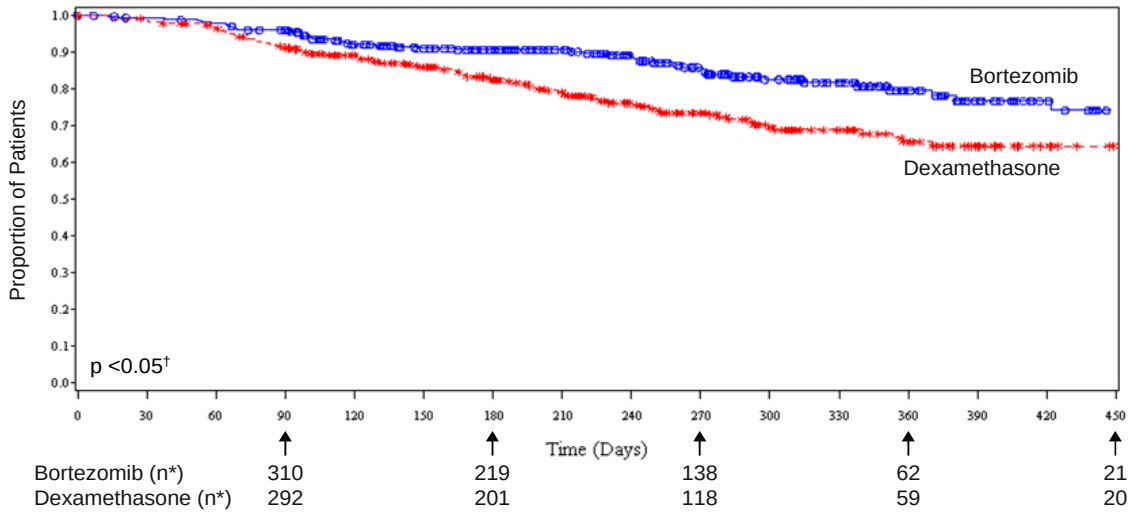
Figure 3: Time to Progression
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

As shown in Figure 4 VELCADE had a significant survival advantage relative to dexamethasone ($p < 0.05$). The median follow-up was 8.3 months.

Figure 4: Overall Survival
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was significantly higher on the VELCADE arm regardless of β_2-microglobulin levels at baseline.

Randomized, Open-Label Clinical Study of VELCADE Subcutaneous vs. Intravenous in Relapsed Multiple Myeloma

An open-label, randomized, phase 3 non-inferiority study compared the efficacy and safety of the subcutaneous administration of VELCADE versus the intravenous administration. This study included 222 bortezomib naïve 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 subcutaneous (n=148) or intravenous (n=74) 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 oral dexamethasone 20 mg daily on the day of and after VELCADE administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade ≥ 2 peripheral neuropathy or neuropathic pain, 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 beta$_2$-microglobulin and albumin levels; Stages I, II, or III).

The baseline demographic and others characteristics of the two treatment groups are summarized as follows: the median age of the patient population was approximately 64 years of age (range 38-88 years), primarily male (subcutaneous: 50%, intravenous: 64%); the primary type of myeloma is IgG (subcutaneous: 65% IgG, 26% IgA, 8% light chain; intravenous: 72% IgG, 19% IgA, 8% light chain), ISS staging I/II/III (%) was 27, 41, 32 for both subcutaneous and intravenous, Karnofsky performance status score was ≤ 70% in 22% of subcutaneous and 16% of intravenous, creatinine clearance was 67.5 mL/min in subcutaneous and 73 mL/min in intravenous, the median years from diagnosis was 2.68 and 2.93 in subcutaneous and intravenous respectively and the proportion of patients with more than one prior line of therapy was 38% in subcutaneous and 35% in intravenous.

This study met its primary (non-inferiority) objective that single agent subcutaneous VELCADE retains at least 60% of the overall response rate after 4 cycles relative to single agent intravenous VELCADE. The results are provided in Table 14.

Table 14: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs. Intravenous

	Subcutaneous VELCADE	Intravenous VELCADE
Intent to Treat Population	**n=148**	**n=74**
Primary Endpoint		
Response Rate at 4 cycles		
ORR (CR+PR) n(%)	63 (43)	31 (42)
Ratio of Response Rates (95% CI)	1.01 (0.73, 1.40)	
CR n (%)	11 (7)	6 (8)
PR n (%)	52 (35)	25 (34)
nCR n (%)	9 (6)	4 (5)
Secondary Endpoints		
Response Rate at 8 cycles		
ORR (CR+PR)	78 (53)	38 (51)
CR n (%)	17 (11)	9 (12)
PR n (%)	61 (41)	29 (39)
nCR n (%)	14 (9)	7 (9)
Median Time to Progression, months	10.4	9.4
Median Progression Free Survival, months	10.2	8.0
1-year Overall Survival (%)[a]	72.6	76.7

[a] Median duration of follow up is 11.8 months

A Randomized Phase 2 Dose-Response Study in Relapsed Multiple Myeloma

An open-label, multicenter study randomized 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy to receive VELCADE 1 mg/m^2 or 1.3 mg/m^2 intravenous bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma and first dose of VELCADE on this trial was 2.0 years, and patients had received a median of 1 prior line of treatment (median of 3 prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

A Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

Patients from the two phase 2 studies, who in the investigators' opinion would experience additional clinical benefit, continued to receive VELCADE beyond 8 cycles on an extension study. Sixty-three (63) patients from the phase 2 multiple myeloma studies were enrolled and received a median of 7 additional cycles of VELCADE therapy for a total median of 14 cycles (range 7 to 32). The overall median dosing intensity was the same in both the parent protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard 3-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. [*see Adverse Reactions (6.1)*]

14.2 Mantle Cell Lymphoma

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 of 155 patients with progressive disease who had received at least 1 prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian.

Of the total, 75% had one or more extra-nodal sites of disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty seven percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for 4 cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity. [*see Dosage and Administration (2.4, 2.5)*]

Responses to VELCADE are shown in Table 15. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was 4; in responding patients the median number of cycles was 8. The median time to response was 40 days (range 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 15: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study

Response Analyses (N = 155)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
Duration of Response	**Median**	**95% CI**
CR + CRu + PR (N = 48)	9.3 months	(5.4, 13.8)
CR + CRu (N = 12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

VELCADE® (bortezomib) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

NDC 63020-049-01
3.5 mg single use vial

Unopened vials may be stored at controlled room temperature 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact[1-4].

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following with patients prior to treatment with VELCADE:

Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Advise patients not to drive or operate machinery if they experience any of these symptoms.

Dehydration/Hypotension: Patients receiving VELCADE therapy may experience vomiting and/or diarrhea. Advise patients how to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Pregnancy/Nursing: Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with VELCADE. Instruct patients to report pregnancy to their physicians immediately. Advise patients that they should not receive VELCADE while pregnant or breast-feeding. If a patient wishes to restart breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician.

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking.

Diabetic Patients: Advise patients to check their blood sugar frequently if using an oral antidiabetic medication and to notify their physicians of any changes in blood sugar level.

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

Other: Instruct patients to contact their physicians if they develop a rash, experience shortness of breath, cough, or swelling of the feet, ankles, or legs, convulsion, persistent headache, reduced eyesight, an increase in blood pressure or blurred vision.

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Rev 13