Velcade adalah obat baru yang terdaftar tahun 2006.
Informasi di bawah ini merupakan informasi update tahun 2008.

JANSSEN-CILAG

Velcade™

bortezomib

COMPOSITION

Velcade (bortezomib) for injection is an antineoplastic agent available for intravenous injection (IV) use only. Each single dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP/EP.

Pharmaceutical Form

Velcade (bortezomib) for injection is supplied as individually cartooned 10 ml vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cell. Inhibition of the 26S proteasome prevents this targeted proteolysis which can affect multiple signaling cascades within the cells. 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.

Clinical Trials

Phase 2 Clinical Studies in Relapsed Multiple Myeloma:

The safety and efficacy of Velcade were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in Table 5.

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

Tabel 5: Summary of Patient Population and Disease Characteristics*

	N = 202

Patient Characteristics	
Median age in years (range)	59 (34,84)
Gender: Male/Female	60% / 40%
Race: Caucasian/black/other	81% / 10% / 8%
Karnofsky Performance Status score = 70	20%
Haemoglobin < 100 g/L	44%
Platelet count < 75 x 10^9/L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β2-microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

*Based on number of patients with baseline data available

Responses to Velcade alone are shown in Table 6. Response rates to Velcade alone were determined by an independent review committee (IRC) based on criteria published by Blade and others.[1] Complete response required <5% plasma cells in the marrow, 100% reduction in M protein, and a negative immunofixation test (IF^-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥ 75% reduction in serum myeloma protein and/or ≥ 90% urine protein.[2] A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

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

mean number of cycles administered was 6.

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

Tabel 6: Summary of Disease Outcomes

Response Analyses (VELCADE monotherapy) N = 188	N (%)	(95% CI)
Overall Response Rate (Blade) (CR + PR)	52 (27.7%)	(21,35)
Complete Response (CR)[1]	5 (2.7%)	(1,6)
Partial Response (PR)[2]	47 (25%)	(19,32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12,24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

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

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

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

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

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

Patients who did not obtain an optimal response to therapy with Velcade alone (progressive or stable disease after 2 or 4 cycles, respectively) were able to receive high-dose dexamethasone in conjunction with Velcade (i.e., 40 mg dexamethasone with each dose of Velcade administered orally as 20 mg on the day of and 20 mg the day after Velcade administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11 and 12), thus 160 mg over 3 weeks). A total of 74 patients were administered dexamethasone in combination with Velcade and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma:
A prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial 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 7.

Table 7: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial

Patient Characteristics	**Velcade N=333**	**Dexamethasone N=336**
Median age in years (range)	62.0 (33,84)	61.0 (27,86)
Gender : male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score = 70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60%/23%/12%	59%/24%/13%
Median β_2-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30mL/min [n(%)]	17(5%)	11(3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%

All Patients	(N=333)	(N=336)
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

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

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

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

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

The time to event analyses and response rates from the phase 3 trial are presented in Table 8. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria.[1] 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^-).

Tabel 8: Summary of Efficacy Analyses in the Randomized Phase 3 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 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (2.8,3.5)
Hazard ratio[b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.97)	
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	
Median Response Duration						
CR[f]	9.9 mo	NE[i]	9.9 mo	NE	6.3 mo	NA
nCR[f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR[f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

a. Kaplan-Meier estimate.
b. Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for Velcade.
c. p-value based on the stratified log-rank test including randomization stratification factors.
d. Precise p-value cannot be rendered.
e. Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug.
f. EBMT criteria[1]; 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 factor;
i. Not Estimable.
j. Not Applicable, no patients in category.

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. Velcade was administered at the recommended dose of 1.3 mg/m^2. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to Velcade are described in table 9.

Table 9: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study

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

* Based on International Response Workshop Criteria (IRWC).

NE = not estimable ** Additional analyses

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

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

Geriatric Use
No overall differences in safety or effectivenees were observed between patients = age 65 and younger patients receiving Velcade; but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic properties
Pharmacokinetics
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours after the 1 mg/m^2 dose and 76-108 hours after 1.3 mg/m^2. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours after the 1 mg/m^2 dose and 76-108 hours after 1.3 mg/m^2. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2, and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Distribution
The mean distribution volume of bortezomib ranged from 489 to 1884 L/m^2 following single or repeat-dose administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.

Metabolism
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

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

Special Populations
Age, Gender and Race
The effects of age, gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment
No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment (see Special Warnings and Special Precautions for Use).

Renal Impairment

No pharmacokinetic studies were conducted with bortezomib in patients with renal impairment. Clinical studies included patients with creatinine clearances values ranging from 13.8 to 220 mL/min (see Special Warnings and Special precautions for Use).

Pediatric

There are no pharmacokinetic data in pediatric patients.

Drug Interactions

No formal drug interaction studies have been conducted with bortezomib.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate of cytocrome P450 3A4, 2C19, and 1A2 (see Special Warnings and Special Precautions for Use).

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6 and 3A4, with IC_{50} values of > 30µM (>11.5 µg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18µM, 6.9 µg/mL) and increase exposure to drugs that are substrates for this enzyme.

Bortezomib did not induced the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

Patients who are concomitantly receiving Velcade and drugs that are inhibitors or inducers of cytochrome P4503A4 should be closely monitored for either toxicities or reduced efficacy.

Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

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

INDICATIONS

Velcade (bortezomib) for injection is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy and have demonstrated disease progression on the last therapy.

Velcade (bortezomib) for injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

POSOLOGY AND METHOD OF ADMINISTRATION

Recommended Dosage

The recommended dose of Velcade is 1.3 mg/m^2/dose administered as a 3 to 5 second bolus

intravenous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Day 12-21).

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

It is recommended that patients with a confirmed complete response receive 2 additional cycles of Velcade beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of Velcade therapy.

Dose Modification and Reinitiation of Therapy

Velcade therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see Special Warnings and Special Precautions for Use). Once the symptoms of the toxicity have resolved, Velcade therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2 dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience Velcade-related neuropathic pain and/or peripheral sensory neuropathy (Table 1). Patients with pre-existing severe neuropathy should be treated with Velcade only after careful risk/benefit assessment.

Table 1: Recommended Dose Modification for Velcade-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

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

NCI Common Toxicity Criteria

Administration

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

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

Peripheral Neuropathy

Velcade treatment causes a peripheral neuropathy that is predominantly sensory. However,

cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported.

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including = Grade 3) during treatment with Velcade. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of Velcade (see Posology and Method of Administration). Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the phase 3 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 studies (see Undesirable Effects). The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

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

Cardiac Disorders
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the phase 3 multiple myeloma study, 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.

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

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

appropriately.

In a clinical trial, two patients given high-dose cytarabine (2g/m^2 per day) by continuous infusion with daunorubicin and Velcade for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.

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

Thrombocytopenia
Velcade is associated with thrombocytopenia (see Undesirable Effects). Platelets were lowest at Day 11 of each cycle of Velcade treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in Table 2 for the phase 3 study. In the phase 3 study, the incidence of significant bleeding events (= Grade 3) was similar on both the Velcade (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to each dose of Velcade. Velcade therapy should be held when the platelet count is <25,000/µL and reinitiated at a reduced dose. (see Posology and Method of Administration and Undesirable Effects). There have been reports of gastrointestinal and intracerebral hemorrhage in association with Velcade. Transfusion may be considered.

Table 2: Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Phase 3 Multiple Myeloma Study

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.

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

Tumor Lysis Syndrome
Because Velcade is a cytotoxic agent and can rapidly kill malignant cells the complications of

tumor lysis syndrome may occur. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Patients with Hepatic Impairment
Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with Velcade.

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

UNDESIRABLE EFFECTS

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

Table 3. Velcade Adverse Drug Reactions in Phase 2 and Phase 3 Multiple Myeloma Studies

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

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

Phostherpetic neuralgia	4 (1%)	1 (<1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (<1%)
Oral Candidiasis	6 (2%)	3 (1%)
Urynary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
Sepsis and bacteremia*	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		
Increased ALT	3 (<1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (<1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%)	18 (8%)
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Neoplasma, benign, malignant, and unspecified (including cysts and polyps)		
Tumor lysis Syndrome	2 (<1%) in study M34101-040‡	-
Nervous system disorders		
Peripheral neuropathy§	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91(27%)	53 (23%)
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (<1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (<1%)	-
Ageusia	2 (<1%)	-
Psychiatric disorders		
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal Impairment and Failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnea	65 (20%)	50 (22%)
Exertional dyspnea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhoea	4 (1%)	14 (6%)
Hemoptysis	3 (<1%)	2 (<1%)

Skin and subcutaneous tissue disorders

Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vaculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petachiae	6 (2%)	7 (3%)
*Cerebral hemorrhage**	1 (<1%)	-

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

*Includes fatal outcome

‡ A study of Velcade at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101 - 039

§ Including all preferred terms under the medDRA HLT "peripheral neurophaty NEC"

Patients with mantle cell lymphoma:

Safety data for patients with mantle cell lymphoma were evaluated in a phase 2 study, which included 155 patients treated with Velcade at the recommended dose of 1.3 mg/m^2. The safety profile of Velcade in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas are peripheral neurophaty, rash and pruruitis were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Post-marketing Experience

Clinically significant adverse events are listed here if they have been reported above.

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with Velcade that met threshold criteria are included in Table 4. The adverse drug reactions are ranked by frequency, using the following convention: Very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10.000 and <1/1000), very rare (<1/10,000, including isolated reports.

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates of incidence that might be obtained in clinical or epidemiological studies.

Table 4: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Rare	**Disseminated intravascular coagulation**
Cardiac Disorders	
Rare	Atrioventricular block complete, cardiac tamponade
Ear and labyrinth disorders	
Rare	**Deafness bilateral**
Eye Disorders	
Rare	Opthalmic herpes
Gastrointestinal Disorders	
Rare	**Ischemic colitis, acute pancreatitis**

Infections and Infestations	
Rare	Herpes meningoencephalitis
Immune System Disorders	
Rare	Angioedema
Nervous System Disorders	
Rare	**Encephalopathy**
Respiratory, thoracic and mediastinal disorders	
Rare	Acute diffuse infiltrative pulmonary diseases, pulmonary hypertension

CONTRAINDICATIONS

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

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal drug interaction studies have been conducted with Velcade. *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate for cytochrome P450 3A4, 2C19, and 1A2. Patients who are concomitantly receiving Velcade and drugs that are inhibitors or inducers of cyctochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy (see Pharmacokinetic properties).

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 adjusment of the dose of their antidiabetic medication.

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

Drug Laboratory Test Interactions

None Known

Pregnancy and Lactation

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

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested 0.075 mg/kg (0.5 mg/m^2) in the rat and 0.05 mg/kg (0.6 mg/m^2) in the rabbit when administered during organogenesis. These dosage 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 0.05 mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

No placental surface transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If Velcade is used during pregnancy,

or if the patients becomes pregnant while receiving this drug, the patient should be apprised of the potential of the potential hazard to the fetus.

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

Nursing Mothers

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

Effects on Ability to Drive and Use Machines

Velcade may be cause tiredness, dizziness, fainting, or blurred vision. Patients should be advise not to drive or operate machinery if they experience these symptoms.

Overdosage

Cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and dead. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

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

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

STORAGE

Velcade contains no antimicrobial preservative. When reconstituted as directed, Velcade may be stored at 25^0C (77^0F). Reconstituted Velcade should be administered within 8 hours of preparations. The reconstituted material may be stored for up to 8 hours in the original vial or in a syringe. The total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

Unopened vials may be stored at controlled room temperature 25^0C (77^0F); excursions premitted from 15 to 30^0C (59 to 86^0F). Retain in original package to protect from light.

Shelf life

36 months

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

Instructions for use, handling and disposal

Administration Precautions

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

Reconstitution/Preparation for intavenous Administration

Prior to use, the contents of each vial must be reconstituted with 3.5 ml of normal (0.9%) saline, sodium chloride injection , USP. The reconstituted product should be a clear and colorless solution.

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

Procedure for Proper Disposal

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

HOW SUPPLIED

Velcade 3.5 mg for injection
Box @ 1 bottle
Reg. No.:DKI0655201744A1

HARUS DENGAN RESEP DOKTER

Manufactured by Ben Venue Laboratories, Inc (BVL), USA
Imported and distriuted by PT. Johnson @ Johnson Indonesia.