Review Report

July 16, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name Velcade Injection 3 mg
Non-proprietary Name Bortezomib (JAN*)
Applicant Janssen Pharmaceutical K.K.
Date of application December 14, 2018
Dosage Form/Strength Lyophilized powder for reconstitution for injection: Each vial contains 3 mg of bortezomib.
Application Classification Prescription drug; (6) Drug with new dosages
Items Warranting Special Mention Orphan drug (Orphan Drug Designation No. 234 [*22 yaku*], PFSB/ELD Notification No. 1110-2, dated November 10, 2010, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare)
Reviewing Office Office of New Drug V

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of untreated multiple myeloma when used in combination with daratumumab (genetical recombination), melphalan, and prednisolone and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

Indications
Multiple myeloma
Mantle cell lymphoma
Primary macroglobulinemia and lymphoplasmacytic lymphoma

(No change)

Dosage and Administration

1. ~~Untreated~~ Multiple myeloma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) by Method A or B described below. At least 72 hours should elapse between doses of Bortezomib.

Method A:

In combination with other antineoplastic drugs, Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated through Cycle 2 or 8. From Cycle 3 or 9 onwards, Bortezomib is administered once weekly for 2 weeks (Days 1 and 8) followed by a 13-day rest period (Days 9 to 21). This 3-week treatment cycle is repeated through Cycle 18. The cycle to switch to the once-weekly regimen should be determined depending on the concomitant antineoplastic drugs.

Method B (for relapsed or refractory multiple myeloma only):

Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. If the therapy needs to be continued for more than 8 cycles, Bortezomib is administered either according to the mentioned schedule or, as maintenance therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) in repeated 5-week cycles.

~~In combination with other antineoplastic drugs, Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42). This 6-week treatment cycle is repeated through Cycle 4. From Cycle 5 onwards, Bortezomib is administered via intravenous or subcutaneous injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42). This 6-week treatment cycle is repeated through Cycle 9. At least 72 hours should elapse between consecutive doses of Bortezomib.~~

~~2. Relapsed or refractory multiple myeloma~~

~~Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. At least 72 hours should elapse between consecutive doses of Bortezomib.~~

~~For extended therapy of more than 8 cycles, Bortezomib is administered on the above dosing schedule or a maintenance schedule of dosing via intravenous or subcutaneous injection once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). This 5-week treatment cycle is repeated.~~

~~3~~2. Mantle cell lymphoma

In combination with other antineoplastic drugs, Bortezomib is administered via intravenous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated through Cycle 6 (or Cycle 8 for patients achieving the first response in Cycle 6). At least 72 hours should elapse between consecutive doses.

Bortezomib can be administered subcutaneously to patients who cannot tolerate intravenous administration.

~~4~~3. Primary macroglobulinemia and lymphoplasmacytic lymphoma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. At least 72 hours should elapse between consecutive doses of bortezomib.

(Underline denotes additions, and strikethrough denotes deletions.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

June 6, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Velcade Injection 3 mg
Non-proprietary Name	Bortezomib
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 14, 2018
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 3 mg of bortezomib.

Proposed Indications

Multiple myeloma
Mantle cell lymphoma
Primary macroglobulinemia and lymphoplasmacytic lymphoma

(No change)

Proposed Dosage and Administration

1. Untreated multiple myeloma

1) Combination therapy with antineoplastic drugs (daratumumab [genetical recombination], melphalan, and prednisolone)

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42). This 6-week period is Cycle 1. From Cycle 2 onwards, Bortezomib is administered via intravenous or subcutaneous injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42). This 6-week treatment cycle is repeated through Cycle 9. At least 72 hours should elapse between consecutive doses of Bortezomib.

2) Combination therapy with other antineoplastic drugs~~,~~

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42). This 6-week treatment cycle is repeated through Cycle 4. From Cycle 5 onwards, Bortezomib is administered via intravenous or subcutaneous injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42). This 6-week treatment cycle is repeated through Cycle 9. At least 72 hours should elapse between consecutive doses of Bortezomib.

2. Relapsed or refractory multiple myeloma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. At least 72 hours should elapse between consecutive doses of Bortezomib.

If the therapy needs to be continued for more than 8 cycles, Bortezomib is administered either according to the mentioned schedule or, as maintenance therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) via intravenous or subcutaneous injection in repeated 5-week cycles.

3. Mantle cell lymphoma

In combination with other antineoplastic drugs, bortezomib is administered via intravenous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated through Cycle 6 (or Cycle 8 for patients achieving the first response in Cycle 6). At least 72 hours should elapse between consecutive doses of bortezomib. Bortezomib can be administered subcutaneously to patients who cannot tolerate intravenous administration.

4. Primary macroglobulinemia and lymphoplasmacytic lymphoma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. At least 72 hours should elapse between consecutive doses of bortezomib.

(Underline denotes additions, and strikethrough denotes deletions)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Summary of product submitted for approval

Bortezomib (INN, bortezomib) is a proteasome inhibitor jointly developed by Millennium Pharmaceuticals and Johnson & Johnson Pharmaceutical Research & Development (currently Janssen Research & Development). Bortezomib binds to the chymotrypsin-like site of the 26S proteasome in the ubiquitin-proteasome system, selectively inhibits the 26S proteasome activity, and subsequently inhibits tumor proliferation via the inhibition of nuclear factor-kappa B (NF-κB) activity.

In Japan, bortezomib was approved for the indication of "relapsed or refractory multiple myeloma" in October 2006. Bortezomib was approved for monotherapy or combination therapy with other antineoplastic drugs for the indication of "multiple myeloma" in September 2011, "mantle cell lymphoma" in June 2015, and "primary macroglobulinemia and lymphoplasmacytic lymphoma" in March 2018.

1.2 Development history etc.

The US Janssen Research & Development started the clinical development of combination therapy of bortezomib with daratumumab (Dara), melphalan and prednisolone or prednisone (MP) (bortezomib/DMP) for untreated multiple myeloma (MM) with a foreign phase I study (Study 1001) in March 2014, followed by a global phase III study (Study 3007) in February 2015.

The use of bortezomib in combination with DMP (bortezomib/DMP) for untreated MM has not been approved in any country or region.

In Japan, the applicant started to enroll patients in Study 3007 in June 2015.

The application of approval for partial change to approved matters (application for partial change) for bortezomib was filed with pivotal study data from Study 3007 to change the dosing regimen for untreated MM.

Bortezomib was designated as an orphan drug with the proposed indication of "newly diagnosed multiple myeloma" in November 2010 (Orphan Drug Designation No. 234 [*22 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application was filed for new dosages, thus no quality-related data were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application was filed for new dosages and the non-clinical pharmacology data were evaluated at the previous review. Accordingly, no new study data were submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application was filed for new dosages and the non-clinical pharmacokinetic data were evaluated at the previous review. Accordingly, no new study data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application was filed for new dosages, thus no toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The present application was filed for new dosages, and the data related to biopharmaceutic studies and associated analytical methods were evaluated at the previous review. Accordingly, no new study data were submitted.

The clinical pharmacology data submitted was the results from Study 1001. The applicant explained that these data demonstrated that DMP does not markedly affect the PK of bortezomib.

Based on the submitted data, PMDA has concluded that the applicant's explanation about the clinical pharmacological profiles of bortezomib is acceptable.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Data from a global phase III study was submitted for the evaluation of the efficacy and safety, and data from a foreign phase Ib study was submitted as reference data (Table 1).

Table 1. List of clinical studies evaluating the efficacy and safety

Data category	Region	Study name	Phase	Subjects	Number of subjects	Outline of dosing regimens	Primary endpoints
Evaluation	Global	Study 3007	III	Patients with untreated MM ineligible for ASCT	680 a) 337 b) 343	a) Bortezomib/DMP was administered. b) Bortezomib/MP was administered.	Efficacy Safety
Reference	Foreign	Study 1001	Ib	Patients with MM	133 a) 6 b) 12 c) 12 d) 103	a) Dara was intravenously administered at 16 mg/kg in combination with bortezomib and dexamethasone (DEX) QW in Cycles 1 and 2 (21-day cycles) and Q3W in Cycle 3 onwards (each cycle consisted of 21 days). b) Dara was intravenously administered at 16 mg/kg in combination with bortezomib/Td QW in Cycles 1 and 2 and Q3W in Cycle 3 onwards (each cycle consisted of 21 days). c) Bortezomib/DMP was administered. d) Dara was intravenously administered at 16 mg/kg in combination with Pd QW in Cycles 1 and 2, Q2W in Cycles 3 to 6, and Q4W in Cycle 7 onwards (each cycles consisted of 28 days).	Safety PK

Dosing regimens for bortezomib/MP and bortezomib/DMP used in individual studies are shown in Table 2.

Table 2. Dosing regimens for bortezomib/MP and bortezomib/DMP

	Dosing regimen
Bortezomib/ MP	Each treatment cycle consisted of 42 days. Bortezomib was administered at 1.3 mg/m^2 subcutaneously (intravenously in patients who could not tolerate subcutaneous administration) on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and Days 1, 8, 22, and 29 of Cycles 2 through 9. Melphalan 9 mg/m^2 and prednisolone or prednisone (not approved in Japan) 60 mg/m^2 were orally administered on Days 1 to 4 of each cycle (for a maximum of 9 cycles).
Bortezomib/ DMP	Each of treatment Cycle 1 through 9 consisted of 42 days. Dara was intravenously administered at 16 mg/kg in combination with bortezomib/MP QW in Cycle 1, Q3W in Cycles 2 through 9, and Q4W in Cycle 10 onwards, each of which consisted of28 days.*1. However, since steroids were administered as prophylaxis for any infusion reactions to Dara (DEX 20 mg or equivalent steroid dose in Study 3007 and methylprednisolone 100 mg or equivalent steroid dose in Study 1001) on Day 1 of each cycle, prednisolone or prednisone (not approved in Japan) was not given on these days.

*1 Dara monotherapy in Cycle 10 onwards was provided only in Study 3007.

Individual studies are summarized below.

The common adverse events other than deaths observed in clinical studies are described in Section "7.2 Adverse events observed in clinical studies." The data from Study 1001 were submitted at the initial application for marketing approval of Dara (see the Review Report for Darzalex Intravenous Infusion 100 mg and 400 mg, dated August 30, 2017), and thus the summary of Study 1001 is omitted in this report.

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1-1: Study 3007 [Ongoing since February 2015 (data cutoff on June 12, 2017)])

An open-label, randomized, controlled study was conducted in patients with untreated MM ineligible for autologous stem cell transplantation (ASCT) (target sample size, 700 patients) at 162 sites in 25 countries and regions including Japan, to compare the efficacy and safety of bortezomib/DMP with those of bortezomib/MP.

Each of Cycles 1 through 9 consisted of 42 days. In the bortezomib/DMP group, Dara was intravenously administered at 16 mg/kg in combination with bortezomib/MP[1)] QW in Cycle 1 and Q3W in Cycles 2 through 9. In Cycle 10 onwards, each of which consisted of 28 days, Dara was intravenously administered at 16 mg/kg Q4W. In the bortezomib/MP group, bortezomib/MP[1)] was administered. Patients in both groups continued to receive treatment until disease progression or any discontinuation criterion met.

A total of 706 patients (350 in the bortezomib/DMP group and 356 in the bortezomib/MP group) were enrolled and randomized in the study. Of these, 26 patients[2)] were excluded because of case deletion, and the remaining 680 patients (337 in the bortezomib/DMP group and 343 in the bortezomib/MP group) were included in the intention-to-treat (ITT) population (Japanese patients, 11 in the bortezomib/DMP group and 13 in the bortezomib/MP group) and were also included in the efficacy analysis set. A total of 674 patients who received

[1)] See Table 2 for dosing regimens.

[2)] All were Japanese patients and were not included in the ITT population because the batch number of bortezomib used in this study could not be identified [see Sections 8.1 and 8.2]. No obvious differences in the efficacy and safety were observed between the population including and excluding these deleted cases.

the study drug (333 in the bortezomib/DMP group and 341 in the bortezomib/MP group) in the ITT population were included in the safety analysis set (Japanese patients, 11 in the bortezomib/DMP group and 13 in the bortezomib/MP group).

The primary endpoint of the study was centrally-assessed progression-free survival (PFS) based on the International Myeloma Working Group (IMWG) response criteria (*Leukemia.* 2006;20:1467-73). An interim analysis for efficacy evaluation was planned to be performed at a time point when the cumulative number of events reached approximately 216 (60% of the target events of 360). The O'Brien-Fleming alpha spending function with the Lan-DeMets method was used to control the Type I error rate associated with the implementation of the interim analysis.

The interim analysis results (data cutoff on June 12, 2017) of centrally-assessed PFS based on the IMWG criteria and their Kaplan-Meier curves are shown in Table 3 and Figure 1, respectively. The superiority of treatment with bortezomib/DMP to bortezomib/MP was verified.[3]

Table 3. Results of PFS analysis (ITT population, centrally-assessed, data cutoff on June 12, 2017)

	Bortezomib/DMP	Bortezomib/MP
Number of subjects	337	343
Number of death or exacerbation (%)	87 (25.8)	141 (41.1)
Median [95% CI] (months)	NE [NE, NE]	17.91 [16.13, 19.81]
Hazard ratio *1 [95% CI]	0.51 [0.39, 0.67]	
p value (two-sided) *2	<0.0001	

*1 Calculated by using a stratified Cox proportional-hazards model with screening disease stage according to the international staging system (ISS) (I, II, and III), region (Europe and other regions), age (<75 years and ≥75 years) as stratifying factors. *2 A stratified log-rank test (with stratifying factors same as those used for the Cox proportional-hazards model), with a two-sided significance level of 0.0097.

3) Based on the PFS results in the population before case deletion (hazard ratio [95% CI]: 0.50 [0.38, 0.65], a p-value [two-sided] of <0.0001, two-sided significance level of 0.0103), the independent data monitoring committee (IDMC) recommended early termination of the study.

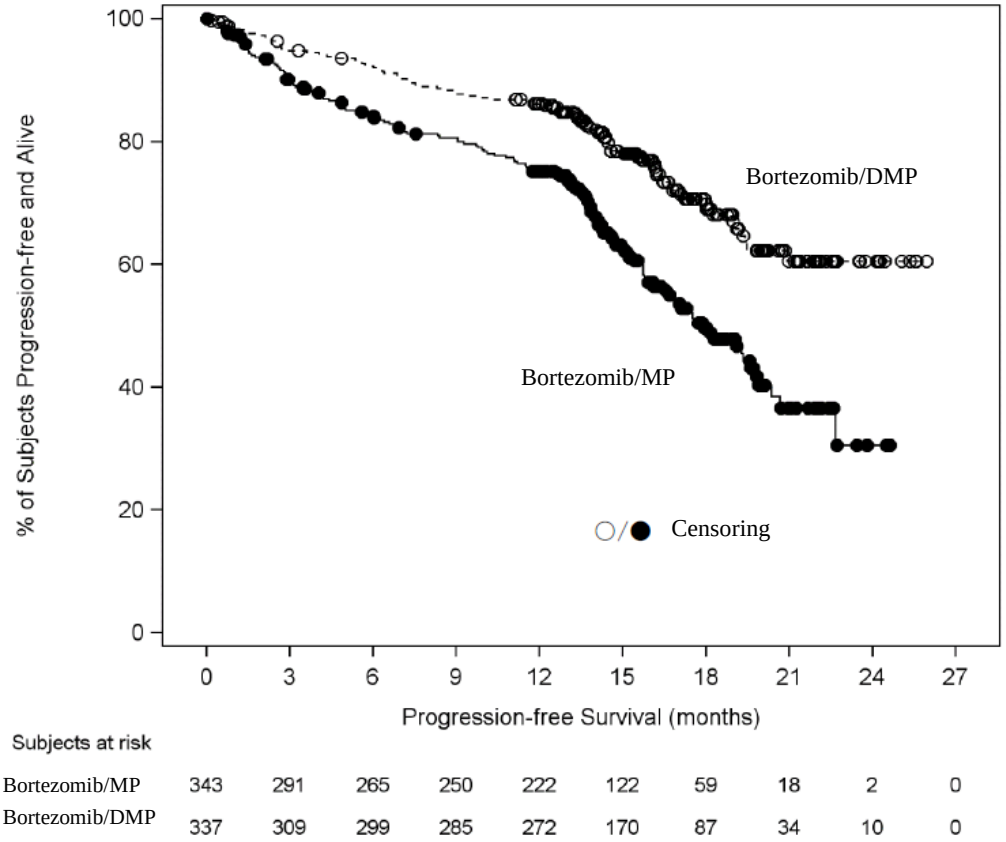

Figure 1. Kaplan-Meier curves for PFS (ITT population, centrally assessed, data cutoff on June 12, 2017)

The safety analysis revealed that deaths occurred during the study treatment period or within 30 days of the last dose in 14 of 333 patients (4.2%) in the bortezomib/DMP group and 16 of 341 patients (4.7%) in the bortezomib/MP group. Causes of death other than disease progression (2 patients in the bortezomib/DMP group and 0 in the bortezomib/MP group) included, in the bortezomib/DMP group, death in 2 patients, pneumonia, acute myocardial infarction, cardiac arrest, acute cardiac failure, intracranial hemorrhage, ischemic stroke, septic shock, tumor lysis syndrome (TLS), upper respiratory tract infection, and intestinal ischemia in 1 patient each; and in the bortezomib/MP group, cardiac arrest and death in 2 patients each, septic shock, TLS, acute kidney injury, anuria, candida sepsis, cardiac failure, cardio-respiratory arrest, cerebral infarction, obstructive airways disorder, pulmonary embolism, sepsis, and traumatic shock in 1 patient each. A causal relationship to the study drug was not ruled out for pneumonia, acute myocardial infarction, and TLS in 1 patient each in the bortezomib/DMP group and pulmonary embolism in 1 patient in the bortezomib/MP group (1 Japanese patient in the bortezomib/MP group died of traumatic shock, and a causal relationship to the study drug was ruled out the event).

7.R Outline of the review conducted by PMDA

7.R.1 Direction of review of data

The present application for partial change was filed to add a dosing regimen of bortezomib for untreated MM, in which the twice-weekly dosing is switched to the once-weekly dosing "from Cycle 2 onwards[4)]" (whereas,

[4)] In 42-day cycles

in the approved dosing regimen, bortezomib is administered twice weekly in Cycles 1 through 4 and once weekly "from Cycle 5 onwards[4)]") in combination therapy with DMP [see Section 7.R.4]. However, data submitted were the results from Study 3007 that was aimed to evaluate the additive effect of Dara to bortezomib/MP administered by the above mentioned dosing regimen in patients with untreated MM.

Accordingly, PMDA decided to review the efficacy and safety of the above-mentioned bortezomib/DMP treatment for patients with untreated MM on the basis of Study 3007 as well as the standard clinical practice guidelines and published literature for hematology and clinical oncology.

7.R.2 Clinical positioning and efficacy

The applicant's explanation about the efficacy of bortezomib/DMP treatment for patients with untreated MM:
In Study 3007, bortezomib/DMP was proven to be superior to bortezomib/MP in the primary endpoint of centrally-assessed PFS based on the IMWG criteria [see Section 7.1.1.1].

The results of centrally-assessed PFS based on the IMWG criteria and their Kaplan-Meier curves at the time of interim analysis in Japanese patients in Study 3007 are shown in Table 4 and Figure 2, respectively.

Table 4. Results of PFS analysis in Japanese subgroup (ITT population, centrally assessed, data cutoff on June 12, 2017)

	Bortezomib/DMP	Bortezomib/MP
Number of subjects	11	13
Number of death or exacerbation (%)	2 (18.2)	5 (38.5)
Median [95% CI] (months)	NE [16.72, NE]	20.67 [9.92, 20.67]
Hazard ratio * [95%CI]	0.39 [0.07, 1.99]	

* Calculated with a non-stratified Cox proportional-hazards model.

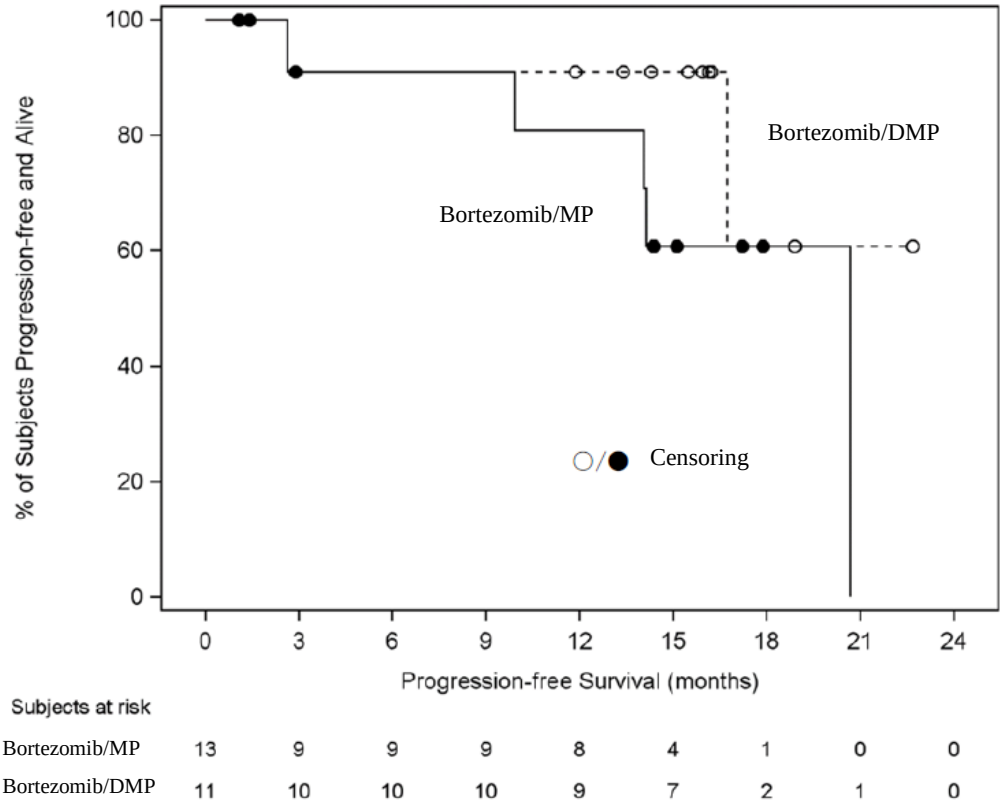

Figure 2. Kaplan-Meier curves for PFS in Japanese subgroup (ITT population, centrally assessed, data cutoff on June 12, 2017)

The clinical practice guidelines in and outside Japan and standard textbooks for hematology and clinical oncology describe bortezomib/DMP for untreated MM as follows.

Clinical practice guidelines

- NCCN guidelines (v2.2019): Treatment with bortezomib/DMP, bortezomib/lenalidomide hydrate and dexamethasone (Ld), or Ld (Category 1[5)]) and treatment with bortezomib/cyclophosphamide hydrate and DEX (Cd) (Category 2A[6)]) are recommended for patients with untreated MM ineligible for ASCT.

Textbooks

- *Wintrobe's Clinical Hematology, 14th Edition* (Lippincott Williams & Wilkins, 2018 USA): Data of comparison of PFS between bortezomib/DMP treatment and bortezomib/MP are shown as a part of the results of the global phase III study (Study 3007) in patients with untreated MM ineligible for ASCT.

These observations indicate that the bortezomib/DMP be recognized as a standard therapy for patients with untreated MM ineligible for ASCT and expected to have a certain level of efficacy.

PMDA accepted the applicant's explanation.

[5)] Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
[6)] Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events observed in clinical studies"]

Based on its review below, PMDA concluded that treatment with bortezomib/DMP in patients with untreated MM ineligible for ASCT requires particular attention to adverse events, e.g., lung disorders, cardiotoxicity, neurotoxicity, hematological toxicity, hypotension, gastrointestinal toxicity, TLS, infections, and HBV reactivation, all of which are known events identified at the previous reviews for the approved indications (see the Review Report for Velcade Injection 3 mg, dated August 10, 2006, the Review Report for Velcade Injection 3 mg, dated August 15, 2011, the Review Report for Velcade Injection 3 mg, dated November 8, 2012, and the Review Report for Velcade Injection 3 mg, dated May 19, 2015).

PMDA has concluded that although caution should be exercised against the above adverse events in the use of bortezomib, bortezomib/DMP is tolerable when adverse events are appropriately monitored and managed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.1 Safety profiles of bortezomib/DMP treatment and differences in the safety of the treatment between Japanese and non-Japanese patients

The applicant provided the following explanation about the safety profiles of bortezomib/DMP and the differences in the safety profiles between Japanese and non-Japanese patients, based on the safety data available from Study 3007 (data cutoff on June 12, 2017).

The safety in Study 3007 is summarized in Table 5.

Table 5. Safety summary (Study 3007)

	Number of subjects (%)					
	Entire study population		Japanese patients		Non-Japanese patients	
	Bortezomib/DMP n = 333	Bortezomib/MP n = 341	Bortezomib/DMP n = 11	Bortezomib/MP n = 13	Bortezomib/DMP n = 322	Bortezomib/MP n = 328
All adverse events	321 (96.4)	329 (96.5)	11 (100)	13 (100)	310 (96.3)	316 (96.3)
Grade ≥3 adverse events	260 (78.1)	264 (77.4)	11 (100)	13 (100)	249 (77.3)	251 (76.5)
Adverse events resulting in death	19 (5.7)	19 (5.6)	1 (9.1)	1 (7.7)	18 (5.6)	18 (5.5)
Serious adverse events	138 (41.4)	113 (33.1)	3 (27.3)	5 (38.5)	135 (41.9)	108 (32.9)
Adverse events leading to treatment discontinuation *1	17 (5.1)	30 (8.8)	2 (18.2)	3 (23.1)	15 (4.7)	27 (8.2)
Adverse events leading to treatment interruption *2	190 (57.1)	157 (46.0)	10 (90.9)	9 (69.2)	180 (55.9)	148 (45.1)
Adverse events leading to dose reduction *3	123 (36.9)	150 (44.0)	5 (45.5)	7 (53.8)	118 (36.6)	143 (43.6)

*1 Discontinuation of all study drugs including bortezomib. *2 Interruption of bortezomib or ≥1 concomitant drug. *3 Dose reduction of bortezomib, melphalan, or prednisolone or prednisone (not yet approved in Japan). No dose reduction criterion was specified for Dara.

In Study 3007, adverse events with a ≥10% higher incidence in the bortezomib/DMP group than in the bortezomib/MP group were upper respiratory tract infection (89 [26.7%] in the bortezomib/DMP group and 49 [14.4%] in the bortezomib/MP group), pneumonia (52 [15.6%] and 17 [5.0%]). A Grade ≥3 adverse event with a ≥5% higher incidence in the bortezomib/DMP group than in the bortezomib/MP group was pneumonia

(39 [11.7%] and 14 [4.1%]). A serious adverse event with a ≥2% higher incidence the bortezomib/DMP group than in the bortezomib/MP group was pneumonia (34 [10.2%] and 11 [3.2%]). Adverse events leading to the interruption the study treatment with a ≥2% higher incidence in the bortezomib/DMP group than in the bortezomib/MP group were thrombocytopenia (47 [14.1%] and 30 [8.8%]), neutropenia (45 [13.5%] and 34 [10.0%]), pneumonia (28 [8.4%] and 5 [1.5%]), upper respiratory tract infection (24 [7.2%] and 9 [2.6%]), bronchitis (14 [4.2%] and 6 [1.8%]), neuralgia (12 [3.6%] and 5 [1.5%]), and anaemia (11 [3.3%] and 3 [0.9%]). An adverse event leading to dose reduction of the study drug with a ≥2% higher incidence in the bortezomib/DMP group than in the bortezomib/MP group was thrombocytopenia (39 [11.7%] and 33 [9.7%]). There were no adverse events with a ≥2% higher incidence in the bortezomib/DMP group than in the bortezomib/MP group that led to the discontinuation of study drug or resulted in death.

In the bortezomib/DMP group of Study 3007, adverse events with a ≥20% higher incidence in the Japanese patients than in non-Japanese patients were leukopenia (10 Japanese patients [90.9%] and 29 non-Japanese patients [9.0%]), thrombocytopenia (9 [81.8%] and 151 [46.9%]), neutropenia (8 [72.7%] and 157 [48.8%]), lymphopenia (8 [72.7%] and 22 [6.8%]), nausea (6 [54.5%] and 60 [18.6%]), injection site erythema (6 [54.5%] and 5 [1.6%]), diarrhoea (5 [45.5%] and 71 [22.0%]), oedema peripheral (5 [45.5%] and 56 [17.4%]), vomiting (4 [36.4%] and 50 [15.5%]), decreased appetite (4 [36.4%] and 32 [9.9%]), and insomnia (3 [27.3%] and 17 [5.3%]). Grade ≥3 adverse events with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients were leukopenia (8 [72.7%] and 13 [4.0%]), lymphopenia (8 [72.7%] and 11 [3.4%]), neutropenia (7 [63.6%] and 124 [38.5%]), thrombocytopenia (7 [63.6%] and 105 [32.6%]), and diarrhoea (2 [18.2%] and 7 [2.2%]). Adverse events leading to dose reduction of the study drug with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients were neutropenia (2 [18.2%] and 21 [6.5%]) and lymphopenia (2 [18.2%] and 0). There were no adverse events with a ≥10% higher incidence in the Japanese patients than in non-Japanese patients that were serious, led to the discontinuation or interruption of study drug, or resulted in death.

PMDA asked the applicant to explain differences in the safety profiles between the bortezomib/MP group in Study 3007 conducted in patients with untreated MM (i.e., bortezomib was administered twice weekly in Cycle 1 and once weekly from Cycle 2 onwards[4)]) and the bortezomib/MP group in the foreign phase III study (VISTA study) in which drugs were administered according to the approved dosing regimen for patients with untreated MM (i.e., bortezomib was administered twice weekly in Cycles 1 through 4 and once weekly from Cycle 5 onwards[4)]).

The applicant's response:
The safety of treatment in the bortezomib/MP group in Study 3007 and the VISTA study[7)] is summarized in Table 6.

[7)] In 42-day cycles, bortezomib 1.3 mg/m^2 was intravenously administered on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycles 1 through 4 and Days 1, 8, 22, and 29 of Cycles 5 through 9, and melphalan 9 mg/m^2 and prednisone (not approved in Japan) 60 mg/m^2 were orally administered on Days 1 to 4 of individual cycles (through Cycle 9).

Table 6. Summary of the safety in the bortezomib/MP group in Study 3007 and the VISTA study

	Number of subjects (%)	
	Study 3007	VISTA study
	Bortezomib/MP n = 341	Bortezomib/MP n = 340
All adverse events	329 (96.5)	338 (99.4)
Grade ≥3 adverse events	264 (77.4)	304 (89.4)
Adverse events resulting in death	19 (5.6)	27 (7.9)
Serious adverse events	113 (33.1)	155 (45.6)
Adverse events leading to treatment discontinuation*1	30 (8.8)	50 (14.7)
Adverse events leading to treatment interruption*2	157 (46.0)	271 (79.7)
Adverse events leading to dose reduction*3	150 (44.0)	188 (55.3)

*1 Discontinuation of all study drugs including bortezomib; *2 Interruption of bortezomib or ≥1 concomitant drug; *3 Dore reduction of bortezomib or at least one concomitant drug

In Study 3007, there were no adverse events of any grade, Grade ≥3, or leading to the treatment interruption or dose reduction of study drug, with a ≥10% higher incidence than in the VISTA study.[8)] In Study 3007, there were no adverse events that were serious, led to the discontinuation of study drug, or resulted in death, with a ≥2% higher incidence than in the VISTA study.

Adverse events with a ≥15% higher incidence in the VISTA study than in Study 3007 were diarrhoea (83 patients [24.3%] in Study 3007 and 157 patients [46.2%] in the VISTA study), nausea (72 [21.1%] and 164 [48.2%]), constipation (62 [18.2%] and 125 [36.8%]), vomiting (53 [15.5%] and 112 [32.9%]), leukopenia (51 [15.0%] and 113 [33.2%]), and neuralgia (16 [4.7%] and 121 [35.6%]). Grade ≥3 adverse events with a ≥10% higher incidence in the VISTA study than in Study 3007 were leukopenia (28 patients [8.2%] in Study 3007 and 77 patients [22.6%] in the VISTA study) and lymphopenia (20 [5.9%] and 67 [19.7%]). Among the adverse events with a ≥2% higher incidence in the VISTA study than in Study 3007, pneumonia (0 in Study 3007 and 7 patients [2.1%] in the VISTA study) resulted in death. Serious adverse events with a ≥2% higher incidence in the VISTA study than in Study 3007 were pneumonia (11 patients [3.2%] in Study 3007 and 37 patients [10.9%] in the VISTA study), thrombocytopenia (4 [1.2%] and 13 [3.8%]), pyrexia (4 [1.2%] and 12 [3.5%]), diarrhoea (2 [0.6%] and 18 [5.3%]), dehydration (1 [0.3%] and 13 [3.8%]), and nausea (1 [0.3%] and 9 [2.6%]). Among the adverse events with a ≥2% higher incidence in the VISTA study than in Study 3007, thrombocytopenia (1 patient [0.3%] in Study 3007 and 10 patients [2.9%] in the VISTA study) led to the discontinuation of study drug. Among the adverse events with a ≥10% higher incidence in the VISTA study than in Study 3007, those leading to the study drug interruption were neutropenia (34 patients [10.0%] in Study 3007 and 89 patients [26.2%] in the VISTA study), thrombocytopenia (30 [8.8%] and 69 [20.3%]), peripheral sensory neuropathy (25 [7.3%] and 63 [18.5%]), neuralgia (5 [1.5%] and 65 [19.1%]), and anaemia (3 [0.9%] and 38 [11.2%]). Among the adverse events with a ≥10% higher incidence in the VISTA study than in Study 3007, neuralgia (11 patients [3.2%] in Study 3007 and 72 patients [21.2%] in the VISTA study) led to dose reduction of the study drug.

8) Adverse events were termed and counted according to the MedDRA/J ver.20.0.

An approximate 10-year gap between Study 3007 and the VISTA study was apparent in different approaches taken in supportive therapy for concurrent diseases, etc., allowing only limited direct comparison of the occurrence of adverse events between the studies. However, the difference in the switching timing from the twice-weekly regimen to the once-weekly regimen raised no significant safety concerns.

PMDA's view:
In Study 3007, some adverse events occurred at a higher incidence in the bortezomib/DMP group than in the bortezomib/MP group, but bortezomib did not cause any new adverse event. PMDA thus concluded that the treatment with bortezomib/DMP is tolerable.

An extremely limited number of Japanese participants in Study 3007 precludes a definite conclusion on the differences in the safety profiles of bortezomib/DMP between Japanese and non-Japanese patients based on the study results. Nevertheless, caution should be exercised against Grade ≥3 adverse events showing a higher incidence in Japanese patients than in non-Japanese patients.

The applicant's explanation about the safety of bortezomib when administered twice weekly in Cycle 1 and once weekly in Cycle 2 onwards[4)] is acceptable.

7.R.4 Dosage and administration

In the present application for partial change, the following dosing regimen of bortezomib was proposed for the bortezomib/DMP therapy for untreated MM, "Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42). This 6-week period is Cycle 1. From Cycle 2 onwards, bortezomib is administered via intravenous or subcutaneous injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42). This 6-week treatment cycle is repeated through Cycle 9. At least 72 hours should elapse between consecutive doses of bortezomib." The "Precautions Concerning Dosage and Administration" section presented the following cautionary advice as with the previously approved dosage regimens.

- Cancer chemotherapy including bortezomib should be selected by physicians based on their accurate understanding of the summary in the "Clinical Studies" section according to the patients' condition and their prior chemotherapy.
- Before the use of bortezomib in combination with other antineoplastic drugs, physicians should carefully read the package inserts of the concomitant drugs.
- The efficacy and safety of bortezomib monotherapy have not been established for untreated MM.
- Guidelines for treatment interruption, dose reduction, treatment discontinuation of bortezomib
- Preparation of injection solution

In view of the discussions presented in Sections "7.R.2 Clinical positioning and efficacy" and "7.R.3 Safety" and the subsection below, PMDA concluded that the "Dosage and Administration" section and the "Precautions Concerning Dosage and Administration" section be described as follows for bortezomib for MM.

Meanwhile, the dosing regimen description for MM was modified in a way that the regimens for untreated MM and for relapsed or refractory MM were combined, while taking into account the existing descriptions of the approved dosing regimens for untreated MM and for relapsed or refractory MM [see Section 7.R.4.1].

Dosage and Administration
Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) by Method A or B described below. At least 72 hours should elapse between consecutive doses of bortezomib.

Method A:
In combination with other antineoplastic drugs, bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated through Cycle 2 or 8. From Cycle 3 or 9 onwards, bortezomib is administered once weekly for 2 weeks (Days 1 and 8) followed by a 13-day rest period (Days 9 to 21). This 3-week treatment cycle is repeated through Cycle 18. The cycle to switch to the once-weekly regimen should be determined depending on the concomitant antineoplastic drugs.

Method B (for relapsed or refractory multiple myeloma only):
Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. If the therapy needs to be continued for more than 8 cycles, bortezomib is administered either according to the mentioned schedule or, as maintenance therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) in repeated 5-week cycles.

Precautions Concerning Dosage and Administration
- The cycle to switch to the once-weekly regimen and antineoplastic drugs to be concomitantly used with bortezomib, etc. should be determined based on an accurate understanding of the summary in the "Clinical Studies" section.
- Before the use of bortezomib in combination with other antineoplastic drugs, physicians should carefully read the package inserts of the concomitant drugs.
- The efficacy and safety of bortezomib monotherapy have not been established for untreated MM.
- Guidelines for treatment interruption, dose reduction, treatment discontinuation of bortezomib
- Preparation of injection solution

7.R.4.1 Dosage and administration of bortezomib

The applicant's explanation about the rationale for the proposed dosing regimen of bortezomib:
For Study 3007, the approved dosing regimen of bortezomib in the bortezomib/MP treatment [9)] was partially modified so that bortezomib be administered twice weekly in Cycle 1 (on Days 1, 4, 8, 11, 22, 25, 29,

[9)] In 42-day cycles, bortezomib was administered on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycles 1 through 4 and Days 1, 8, 22, and 29 of Cycles 5 through 9.

and 32 of 42 days) and once weekly in Cycles 2 onwards (on Days 1, 8, 22, and 29 of 42 days) for the following reasons.

- A foreign clinical study of bortezomib/MP was conducted in patients with untreated MM ineligible for ASCT (Study GEM2005MAS65). In the study, bortezomib was administered twice weekly in Cycle 1 (42-day cycle) and once weekly in Cycle 2 onwards (35-day cycles). The dosing regimen of Study GEM2005MAS65 showed no clear differences in the efficacy as compared to the approved dosing regimen[9)] but alleviated peripheral neuropathy (*Lancet Oncol.* 2010;11:934-41).
- The Japanese guidelines (e.g., the Practical guidelines for hematological malignancies 2013 edited by the Japanese Society of Hematology) recommend the once-weekly regimen of bortezomib in bortezomib/MP treatment as a standard treatment for patients with untreated MM ineligible for ASCT.
- A foreign textbook (*Wintrobe's Clinical Hematology, 13th Edition*. [Lippincott Williams & Wilkins, 2013, USA]) describes that, based on data from studies in elderly patients, switching the bortezomib regimen from twice weekly to once weekly in bortezomib/MP treatment contributes not only to greater feasibility and efficacy of treatment but also to alleviated peripheral neuropathy.

Study 3007 with the above mentioned design and demonstrated the clinical benefits of bortezomib for patients with untreated MM [see Sections 7.R.2 and 7.R.3]. Therefore, the dosing regimen of bortezomib in the bortezomib/DMP treatment in patients with untreated MM was proposed on the basis of the dosing regimen used in the study.

PMDA's view:
It is acceptable that the dosing regimen in the bortezomib/DMP treatment for patients with untreated MM was determined on the basis of the dosing regimen of bortezomib used in Study 3007. There are no evidence of clinical benefits of the bortezomib dosing regimen in the bortezomib/MP treatment, in which bortezomib was administered twice weekly in Cycle 1 and once weekly in Cycle 2 onwards in 42-day cycles. However, the regimen is expected to have a certain extent of clinical benefits in light of the observations below and the applicant's explanation about the dosing regimen in Study 3007. Thus, there is less need to completely remove the bortezomib/MP treatment from the dosing regimens of bortezomib, on the premise that bortezomib be appropriately prescribed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

- In Study 3007, the response rate was 73% in the bortezomib/MP group, in which bortezomib was administered once weekly from Cycle 2 onwards.[4)] In the VISTA study, the response rate was 71% in the bortezomib/MP group in which bortezomib was administered once weekly from Cycle 5 onwards.[4)] The studies found no obvious difference in the response rates or raised no significant safety concerns [see Section 7.R.3.1].
- The standard clinical practice guidelines and published literature in and outside Japan recommend the once-weekly dosing of bortezomib/MP.

In light of the above discussion and the following statements about the approved dosing regimens of bortezomib for untreated MM and for relapsed or refractory MM, the "Dosage and Administration" section of the package insert should present the bortezomib dosing regimens for untreated MM and relapsed or refractory MM in a combined manner as below, along with information provided in the "Clinical Studies" section, including the antineoplastic drugs used with bortezomib in the clinical studies and the cycle to switch to the once-weekly regimen, as well as cautionary advice in the "Precautions Concerning Dosage and Administration" section shown further below.

- For the approved dosing regimen of bortezomib/MP for untreated MM, the "Precautions Concerning Dosage and Administration" section of the package insert highlights that bortezomib should be administered in combination with other antineoplastic drugs, on the premise that cancer chemotherapy including bortezomib be selected by physicians based on their accurate understanding of the summary in the "Clinical Studies" section, and according to the patients' condition and their prior chemotherapy (see the Review Report for Velcade Injection 3 mg, dated August 15, 2011).
- For the dosing regimen of bortezomib for relapsed or refractory MM, the cycle to switch from the twice weekly regimen to the once weekly regimen is defined on a basis of a 3-week (21 days) cycles, instead of 6-week (42 days) cycles.

Dosage and Administration

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) by Method A or B described below. At least 72 hours should elapse between consecutive doses of bortezomib.

Method A:

In combination with other antineoplastic drugs, bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated through Cycle 2 or 8. From Cycle 3 or 9 onwards, bortezomib is administered once weekly for 2 weeks (Days 1 and 8) followed by a 13-day rest period (Days 9 to 21). This 3-week treatment cycle is repeated through Cycle 18. The cycle to switch to the once weekly regimen should be determined depending on the concomitant antineoplastic drugs.

Method B (for relapsed or refractory multiple myeloma only):

Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. If the therapy needs to be continued for more than 8 cycles, bortezomib is administered either according to the mentioned schedule or, as maintenance therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) in repeated 5-week cycles.

Precautions Concerning Dosage and Administration

- The cycle to switch to the once-weekly regimen and antineoplastic drugs to be concomitantly used with

bortezomib, etc. should be determined based on an accurate understanding of the summary in the "Clinical Studies" section.

- Before the use of bortezomib in combination with other antineoplastic drugs, physicians should carefully read the package inserts of the concomitant drugs.
- The efficacy and safety of bortezomib monotherapy have not been established for untreated MM.
- Guidelines for treatment interruption, dose reduction, treatment discontinuation of bortezomib
- Preparation of injection solution

7.R.5 Post-marketing investigations

The applicant's explanation about post-marketing safety information:

Because no safety issues of concerns were identified in the present application for partial change, the applicant considered that there would be no need to conduct post-marketing surveillance immediately after approval for the safety evaluation of bortezomib/DM in patients with untreated MM based on the following observations. Instead, the applicant intended to collect safety information through routine pharmacovigilance activities.

- No clear differences were observed in the safety profiles between the bortezomib treatment in Study 3007 and the bortezomib treatment for the approved indication.
- Post-marketing surveillance has been conducted in patients with MM, through which a certain amount of safety data of bortezomib has been collected from Japanese patients.

PMDA accepted the applicant's explanation.

7.2 Adverse events observed in clinical studies

Deaths reported in the clinical study data which were submitted to evaluate the safety are described in Section "7.1 Evaluation data," and common adverse events other than death are summarized below.

7.2.1 Global phase III study (Study 3007)

Adverse events occurred in 321 of 333 patients (96.4%) in the bortezomib/DMP group and 329 of 341 patients (96.5%) in the bortezomib/MP group. A causal relationship to the study drug could not be ruled out for events occurring in 294 of 333 patients (88.3%) in the bortezomib/DMP group and 290 of 341 patients (85.0%) in the bortezomib/MP group. Adverse events with an incidence of ≥15% in either group are shown in Table 7.

Table 7. Adverse events with an incidence of ≥15% in either group

SOC PT (MedDRA/J ver.20.0)	Number of subjects (%)			
	Bortezomib/DMP n = 333		Bortezomib/MP n = 341	
	All grades	Grades ≥3	All grades	Grade ≥ 3
All adverse events	321 (96.4)	260 (78.1)	329 (96.5)	264 (77.4)
Blood and lymphatic system disorders				
Neutropenia	165 (49.5)	131 (39.3)	181 (53.1)	132 (38.7)
Thrombocytopenia	160 (48.0)	112 (33.6)	182 (53.4)	128 (37.5)
Anaemia	95 (28.5)	54 (16.2)	130 (38.1)	67 (19.6)
Leukopenia	39 (11.7)	21 (6.3)	51 (15.0)	28 (8.2)
Infections and infestations				
Upper respiratory tract infection	89 (26.7)	7 (2.1)	49 (14.4)	5 (1.5)

SOC PT (MedDRA/J ver.20.0)	Number of subjects (%)			
	Bortezomib/DMP n = 333		Bortezomib/MP n = 341	
	All grades	Grades ≥3	All grades	Grade ≥ 3
All adverse events	321 (96.4)	260 (78.1)	329 (96.5)	264 (77.4)
Pneumonia	52 (15.6)	39 (11.7)	17 (5.0)	14 (4.1)
General disorders and administration site conditions				
Pyrexia	73 (21.9)	2 (0.6)	65 (19.1)	1 (0.3)
Oedema peripheral	61 (18.3)	3 (0.9)	38 (11.1)	1 (0.3)
Gastrointestinal disorders				
Diarrhoea	76 (22.8)	9 (2.7)	83 (24.3)	11 (3.2)
Nausea	66 (19.8)	3 (0.9)	72 (21.1)	4 (1.2)
Constipation	60 (18.0)	3 (0.9)	62 (18.2)	1 (0.3)
Vomiting	54 (16.2)	5 (1.5)	53 (15.5)	6 (1.8)
Nervous system disorders				
Peripheral sensory neuropathy	95 (28.5)	5 (1.5)	118 (34.6)	14 (4.1)
Respiratory, thoracic and mediastinal disorders				
Cough	51 (15.3)	1 (0.3)	25 (7.3)	1 (0.3)

Serious adverse events occurred in 138 of 333 patients (41.4%) in the bortezomib/DMP group and 113 of 341 patients (33.1%) in the bortezomib/MP group. The following serious adverse events occurred in ≥7 patients in individual groups: in the bortezomib/DMP group, pneumonia in 34 patients (10.2%), bronchitis in 8 patients (2.4%), lower respiratory tract infection in 8 patients (2.4%), and upper respiratory tract infection in 7 patients (2.1%); and in the bortezomib/MP group, pneumonia in 11 patients (3.2%), anaemia in 9 patients (2.6%), febrile neutropenia in 7 patients (2.1%), and cardiac failure in 7 patients (2.1%). A causal relationship with the study drug was not ruled out for pneumonia in 10 patients, bronchitis and lower respiratory tract infection in 3 patients each, and upper respiratory tract infection 2 patients in the bortezomib/DMP group; febrile neutropenia in 7 patients, pneumonia and anaemia in 4 patients each, and cardiac failure in 2 patients in the bortezomib/MP group.

Adverse events led to the discontinuation of study drug in 17 of 333 patients (5.1%) in the bortezomib/DMP group and 30 of 341 patients (8.8%) in the bortezomib/MP group. Among adverse events occurring in ≥7 patients in each group, none led to the discontinuation of study drug.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection revealed missing records such as the batch numbers of bortezomib administered to some patients in Study 3007 (CTD 5.3.5.1.1-1), which would be necessary for traceability in terms of quality assurance. For this reason, PMDA decided that the review be conducted after any measures taken, e.g., the removal of affected portions of study data from the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection revealed non-conformity with the GCP at the sponsor. PMDA concluded that the sponsor would need to take appropriate measures, i.e., the removal of affected case data from the application documents submitted, but there would be no obstacles to proceeding with its review based on the documents excluding the case data subject to deletion. The inspection also identified the following errors at the sponsor, although they had no significant impacts on the overall assessment of the studies. The errors were notified to the sponsor to seek corrective actions.

Non-conformity with the GCP

Sponsor

- Some case reports had missing records such as the batch numbers of bortezomib, which would be necessary for traceability to assure the quality of bortezomib administered.

Findings requiring corrective action

Sponsor

- Bortezomib was not managed or handled as a study drug.
- The study protocol did not provide appropriate briefing on bortezomib, even though which was a study drug focused in the clinical study.
- The investigator's brochure of bortezomib was not provided to the heads of study sites.
- There was no documented procedure for the management of bortezomib as a study drug.
- The annual report on the safety of bortezomib was not appropriately provided to the investigators and the heads of study sites.
- Information including unexpected serious adverse reactions to bortezomib was not appropriately provided to the investigators and the heads of study sites.

9. Overall Evaluation during Preparation of the Review Report (1)

Based on the data submitted, PMDA has concluded that the treatment with bortezomib/DMP has efficacy in the treatment of untreated MM and that the treatment with bortezomib/DMP has acceptable safety in view of its benefits. Bortezomib/DMP treatment is clinically meaningful because it offers a new treatment option for patients with untreated MM. PMDA considers that the clinical positioning and dosing regimen of bortezomib/DMP treatment be further evaluated.

PMDA has concluded that bortezomib may be approved if bortezomib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 12, 2019

Product Submitted for Approval

Brand Name	Velcade Injection 3 mg
Non-proprietary Name	Bortezomib
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 14, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review in Section "7.R.2 Clinical positioning and efficacy" of the Review Report (1), PMDA concluded that the treatment with bortezomib/DMP is expected to have a certain extent of efficacy in patients with untreated MM ineligible for ASCT in light of data available from a global phase III study conducted in untreated MM ineligible for ASCT (Study 3007).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of its review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that the treatment with bortezomib/DMP in patients with untreated MM ineligible for ASCT requires particular attention to adverse events, namely, lung disorders, cardiotoxicity, neurotoxicity, hematological toxicity, hypotension, gastrointestinal toxicity, TLS, infections, and HBV reactivation, which are known events identified during the previous review for the approved indication.

PMDA further concluded that although caution should be exercised against the above adverse events during the treatment with bortezomib/DMP, bortezomib/DMP is tolerable when adverse events are appropriately monitored and managed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Dosage and administration

As a result of its review in Section "7.R.4 Dosage and administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" section and the "Precautions Concerning Dosage and Administration" section of the package insert of bortezomib should be described as follows.

Dosage and Administration

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) by Method A or B described below. At least 72 hours should elapse between consecutive doses of bortezomib.

Method A:

In combination with other antineoplastic drugs, bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated through Cycle 2 or 8. From Cycle 3 or 9 onwards, bortezomib is administered once weekly for 2 weeks (Days 1 and 8) followed by a 13-day rest period (Days 9 to 21). This 3-week cycle is repeated through Cycle 18. The cycle to switch to the once-weekly regimen should be determined depending on the concomitant antineoplastic drugs.

Method B (for relapsed or refractory multiple myeloma only):

Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated. If the therapy needs to be continued for more than 8 cycles, bortezomib is administered either according to the mentioned schedule or, as maintenance therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) in repeated 5-week cycles.

Precautions Concerning Dosage and Administration

- The cycle to switch to the once-weekly regimen and antineoplastic drugs to be concomitantly used with bortezomib, etc. should be determined based on an accurate understanding of the summary in the "Clinical Studies" section.
- Before the use of bortezomib in combination with other antineoplastic drugs, physicians should carefully read the package inserts of the concomitant drugs.
- The efficacy and safety of bortezomib monotherapy have not been established for untreated MM.
- Guidelines for treatment interruption, dose reduction, treatment discontinuation of bortezomib
- Preparation of injection solution

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to refine the descriptions in the "Dosage and Administration" and the "Precautions Concerning Dosage and Administration" sections as above. The applicant agreed.

1.4 Risk management plan (draft)

In view of the discussions presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1), PMDA considers that it is not necessary to conduct post-marketing surveillance immediately after approval for the safety evaluation of bortezomib/DMP in patients with untreated MM and that safety data be collected through routine pharmacovigilance activities.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and the modified dosage regimens presented below. The approval however is based on the premise of appropriate cautionary advice given via the package insert and information provided on the proper use of bortezomib in the post-marketing setting, as well as adherence to the proper use of bortezomib under the supervision of physicians with adequate knowledge and experience in treatment of hematopoietic malignancies at medical facilities adequately capable of dealing with emergency cases.

Indications (No change)

Multiple myeloma
Mantle cell lymphoma
Primary macroglobulinemia and lymphoplasmacytic lymphoma

Dosage and administration (Underline denotes additions, and strikethrough denotes deletions)

1. ~~Untreated m~~Multiple myeloma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) by Method A or B described below. At least 72 hours should elapse between consecutive doses of bortezomib.

Method A:

In combination with other antineoplastic drugs, bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated through Cycle 2 or 8. From Cycle 3 or 9 onwards, bortezomib is administered once weekly for 2 weeks (Days 1 and 8) followed by a 13-day rest period (Days 9 to 21). This 3-week cycle is repeated through Cycle 18. The cycle to switch to the once-weekly regimen should be determined depending on the concomitant antineoplastic drugs.

Method B (for relapsed or refractory multiple myeloma only):

Bortezomib is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated. If the therapy needs to be continued for more than 8 cycles, bortezomib is administered either according to the mentioned schedule or, as maintenance

therapy, once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) in repeated 5-week cycles.

~~In combination with other antineoplastic drugs, bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, 11, 22, 25, 29, and 32 followed by a 10-day rest period (Days 33 to 42). This 6-week treatment cycle is repeated to Cycle 4. From Cycle 5 onwards, bortezomib is administered via intravenous or subcutaneous injection on Days 1, 8, 22, and 29 followed by a 13-day rest period (Days 30 to 42). This 6-week treatment cycle is repeated to Cycle 9. At least 72 hours should elapse between consecutive doses of bortezomib.~~

~~2. Relapsed or refractory multiple myeloma~~

~~Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week treatment cycle is repeated. At least 72 hours should elapse between consecutive doses of bortezomib.~~

~~For extended therapy of more than 8 cycles, bortezomib is administered on the above dosing schedule or a maintenance schedule of dosing via intravenous or subcutaneous injection once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). This 5-week treatment cycle is repeated.~~

~~3~~2. Mantle cell lymphoma

In combination with other antineoplastic drugs, bortezomib is administered via intravenous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated through Cycle 6 (or Cycle 8 for patients achieving the first response in Cycle 6). At least 72 hours should elapse between consecutive doses of bortezomib. Bortezomib can be administered subcutaneously to patients who cannot tolerate intravenous administration.

~~4~~3. Primary macroglobulinemia and lymphoplasmacytic lymphoma

Bortezomib is administered via intravenous or subcutaneous injection at a usual adult dose of 1.3 mg/m^2 (body surface area) on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). This 3-week cycle is repeated. At least 72 hours should elapse between consecutive doses of bortezomib.

Warning (No change)

1. Bortezomib should be used only in patients who are considered eligible for the treatment under the supervision of physicians with adequate knowledge and experience in hematopoietic malignancies at medical institutions with adequate facilities for treatment of emergencies. Prior to the start of treatment, the patient or his/her family should be fully informed about the benefits and risks associated with the treatment. The treatment should be started only after consent is obtained from the patient or his/her family.
2. In the initial phase of the treatment, patients should be hospitalized and treated appropriately under the supervision of physicians.
3. A death from a lung disorder (interstitial pneumonia) was reported from a clinical study in Japan, and a causal relationship with bortezomib could not be ruled out for the event. Though rare outside Japan, lung disorders (e.g., interstitial pneumonia, pulmonary edema, acute respiratory distress syndrome, and pleural

effusion) for which a causal relationship to bortezomib cannot be ruled out may occur more frequently in Japan, and the following advice thus warrants special attention:

1) Before starting the treatment with bortezomib, radiography or computed tomography images should be checked for any abnormalities in the chest, based on which whether to start the treatment should be determined.
2) Patients should be carefully monitored for symptoms e.g., shortness of breath, dyspnea, cough, and pyrexia, and abnormalities in chest auscultatory findings, respiratory rate, etc., during and after bortezomib treatment, particularly early after the start of the treatment. Arterial oxygen saturation and chest computed tomography images should be checked as necessary to monitor the clinical course. In case of a lung disorder with a suspected association with bortezomib, the treatment should be discontinued or any appropriate measure should be taken.

4. Physicians should carefully read the package insert, etc. prior to the use of bortezomib.

Contraindication (No change)

Patients with a history of hypersensitivity to bortezomib, mannitol, or boron.

Precautions Concerning Indications (No change)

For treatment of multiple myeloma or mantle cell lymphoma, eligible patients must be selected by physicians familiar with the efficacy and safety of bortezomib based on an accurate understanding of the summary in the "Clinical Studies" section.

Precautions Concerning Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions)

1. For multiple myeloma, the cycle to switch to the once-weekly regimen and antineoplastic drugs to be concomitantly used with bortezomib, etc. should be determined based on an accurate understanding of the summary in the "Clinical Studies" section.
2. For mantle cell lymphoma, cancer chemotherapy including bortezomib should be selected based on an accurate understanding of the summary in the "Clinical Studies" section, and according to the patients' condition and prior chemotherapy.
~~2~~3. Before the use of bortezomib in combination with other antineoplastic drugs, physicians should carefully read the package insert of the concomitant drugs.
~~3~~4. The efficacy and safety of bortezomib monotherapy have not been established for untreated multiple myeloma and mantle cell lymphoma.
~~4~~5. No clinical study data are available on subcutaneous dose of bortezomib in patients with mantle cell lymphoma.
~~5~~6. For treatment with bortezomib, the decision on the dose reduction, treatment interruption, or treatment discontinuation should be made appropriately according to the following guidelines:
   1) Dose modifications for multiple myeloma, primary macroglobulinemia, and lymphoplasmacytic lymphoma
      (1) Grade 3/4* adverse drug reactions (excluding peripheral neuropathy and neuropathic pain)

If a Grade ≥3 nonhematological toxicity (excluding peripheral neuropathy and neuropathic pain) or Grade 4 hematological toxicity occurs, interrupt bortezomib until recovery of symptoms. Bortezomib may be resumed with due consideration of its risks and benefits, at a reduced dose according to the guidelines in the table below. If the adverse reaction shows no improvement or recurs even at the lowest dose (0.7 mg/m^2), consider the discontinuation of bortezomib.

Dose reduction guidelines following a Grade 3/4 adverse reactions of (excluding peripheral neuropathy and neuropathic pain)

Dose at the onset of adverse drug reactions	Dose reduced to
1.3 mg/m^2	1.0 mg/m^2
1.0 mg/m^2	0.7 mg/m^2
0.7 mg/m^2	Discontinue bortezomib

*The National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v4.0

(2) Peripheral neuropathy or neuropathic pain

If the event is likely attributable to bortezomib, interrupt or discontinue bortezomib, or reduce the bortezomib dose according to the guidelines in the table below.

Dose adjustment guidelines for peripheral neuropathy or neuropathic pain

NCI-CTCAE Grade* (symptoms)	Dosage and dose modification
Grade 1 without pain or loss of function (asymptomatic; loss of deep tendon reflexes or paresthesia)	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limited instrumental activities of daily living)	Reduce the dose from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2.
Grade 2 with pain or Grade 3 (severe symptoms; limited self-care activities of daily living)	Withhold bortezomib until recovery. After recovery, resume bortezomib at the reduced dose of 0.7 mg/m^2 once per week.
Grade 4 (life-threatening ; requiring emergency treatment)	Discontinue bortezomib.

*NCI-CTCAE v4.0

2) Dose modifications for mantle cell lymphoma

Prior to the start of new cycle of bortezomib treatment, confirm that:

- The platelet count is ≥100,000/μL, neutrophil count is ≥1,500/μL, and hemoglobin level is ≥8 g/dL.
- Nonhematological toxicities have improved to Grade 1* or baseline level.

Dose adjustment guidelines following an adverse drug reaction

Adverse drug reactions	Dosage and dose modification
Grade ≥3 neutropenia with fever, Grade 4 neutropenia persisting for 7 days, or platelet count of <10,000/μL	Withhold bortezomib for up to 2 weeks until recovery of neutrophil count to ≥750/μL and the platelet count to ≥25,000/μL. • If the adverse drug reaction does not recover to these levels after the interruption, discontinue bortezomib. • If the adverse drug reaction shows recovery to these levels, resume bortezomib at the 1-level lower dose (from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2).
Platelet count of <25,000/μL or neutrophil count of <750/μL on the day of bortezomib administration (other than Day 1 of each cycle)	Delay the bortezomib dose for up to 2 days. Withhold bortezomib if the dose needs to be delayed for of >2 days.
Grade ≥3 nonhematological toxicity (excluding peripheral neuropathy and neuropathic pain)	Withhold bortezomib until recovery of toxicity to ≤Grade 2. After recovery, resume bortezomib at 1-level lower dose (from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2).
Peripheral neuropathy or neuropathic pain	See "~~5~~6. 1) (2) Peripheral neuropathy or neuropathic pain."

*NCI-CTCAE v4.0

~~6~~7. Preparation of injection solution

1) Intravenous dose

Reconstitute the content of each vial with 3.0 mL of isotonic sodium chloride solution (Japanese Pharmacopoeia).

2) Subcutaneous dose

Reconstitute the content of each vial with 1.2 mL of isotonic sodium chloride solution (Japanese Pharmacopoeia).

Preparation of injection solution

Route of administration	Bortezomib (mg/vial)	Isotonic sodium chloride solution (Japanese Pharmacopoeia)	Final bortezomib concentration
Intravenous	3.0 mg	3.0 mL	1.0 mg/mL
Subcutaneous	3.0 mg	1.2 mL	2.5 mg/mL

Appendix

List of Abbreviations

Application for partial change	application for approval of partial changes to approved matters
ASCT	autologous stem cell transplantation
bortezomib	bortezomib
bortezomib/Cd	combination of bortezomib with Cd
bortezomib/DEX	combination of bortezomib with DEX
bortezomib/DMP	combination of bortezomib with DMP
bortezomib/Ld	combination of bortezomib with Ld
bortezomib/MP	combination of bortezomib with MP
bortezomib/Td	combination of bortezomib with Td
Cd	combination of cyclophosphamide hydrate with DEX
CI	confidence interval
Dara	daratumumab (genetical recombination)
DEX	dexamethasone
DMP	combination of Dara with MP
HBV	hepatitis B virus
IDMC	independent data monitoring committee
IMWG	International Myeloma Working Group
IMWG criteria	evaluation criteria developed by the IMWG
ISS	international staging system
ITT	intent-to-treat
Ld	combination of lenalidomide hydrate with DEX
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
MP	combination of melphalan with prednisolone or prednisone (not approved in Japan)
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NE	not estimable
NF-κB	nuclear factor-kappa B
OS	overall survival
Pd	combination of pomalidomide with DEX
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
QW	quaque 1 week
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
SOC	system organ class
Study 1001	Study 54767414MMY1001
Study 3007	Study 54767414MMY3007
Td	combination of thalidomide with DEX
TLS	tumor lysis syndrome
VISTA Study	Study 26866138-MMY-3002